SAAG AND PLATELET COUNT/SPLENIC DIAMETER RATIO AS NON INVASIVE PREDICTORS OF ESOPHAGEAL VARICES IN CIRRHOSIS

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CERTIFICATE

This is to certify that the dissertation titled **"SAAG AND PLATELET COUNT/SPLENIC DIAMETER RATIO AS NONINVASIVE PREDICTORS OF ESOPHAGEAL VARICES IN CIRRHOSIS"** is the bonafide original work of DR. DEEPAK NANDAN in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in March 2007. The Period of study was from August 2005 to July 2006.

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DECLARATION

I, **DR. DEEPAK NANDAN ,** solemnly declare that dissertation titled **"SAAG AND PLATELET COUNT/SPLENIC DIAMETER RATIO AS NONINVASIVE PREDICTORS OF ESOPHAGEAL VARICES IN CIRRHOSIS"** is a bonafide work done by me at Govt. Stanley Medical College and Hospital during August 2005- July 2006 under guidance and supervision of my unit chief Prof. T. VENKATAKRISHNAN., Addl. Professor of Medicine**.**

This dissertation is submitted to Tamilnadu DR. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine.**

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CONTENTS

INTRODUCTION

Portal hypertension commonly accompanies the presence of liver cirrhosis, and the development of esophageal varices is one of the major complications of portal hypertension. The prevalence of esophageal varices in patients with liver cirrhosis may range from 60% to 80%, and the reported mortality from variceal bleeding ranges from 17% to 57%. Cirrhotic patients with Portal Hypertension who develop esophageal varices are at a very high risk of variceal bleeding and Variceal rupture is a common cause of death in cirrhosis.

Esophageal varices appear only after the hepatic venous pressure gradient (HVPG) has increased to at least 10 to 12 mm Hg.1/3 of gastrointestinal bleedings reveal pre-existent cirrhosis. In patients with cirrhosis the incidence of esophageal varices increases by nearly 5% per year, and the rate of progression from small to large varices is approximately 5 to 10 % per year. The risk of variceal rupture is greatest in the 2 years following diagnosis.

In the 2 years following the first detection of esophageal varices , risk of variceal bleeding ranges between 20% to 30% and results in a mortality of 25% to 50% within a week of the first bleeding episode. Therefore, portal hypertensive bleeding prevention remains at the forefront of the long-term management of cirrhotic patients. As there is clear evidence that primary

prevention of variceal rupture is cost effective in reducing death rate, screening for esophageal varices (EV) is recommended.

Prophylactic treatment in patients with non selective Beta blockers in varices that has never bled appears to decrease the incidence of bleeding by 40 to 50 % and prolong survival. So endoscopic screening for varices in patients with cirrhosis is desirable, some have suggested this should be repeated every other year.

The American Association for the Study of Liver Disease single topic symposium 1996 stated that cirrhotic patients should be screened for the presence of esophageal varices when portal hypertension is diagnosed. Recently, the Baveno III Consensus Conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of esophageal varices when liver cirrhosis is diagnosed. Other authors have suggested repeating endoscopy at 2–3 year intervals in patients without varices and at 1–2 year intervals in patients with small varices and every other year in patients with decompensated liver disease so as to evaluate the development or progression of this feature.

Endoscopic screening may take place under two circumstances: at the initial diagnosis of cirrhosis, since esophageal varices are an independent predictive factor and an early complication of cirrhosis, and during the follow-up of patients with cirrhosis without esophageal varices at risk of bleeding at first examination with or without decompensation.

It has been estimated that it is only the large esophageal varices (LEV), which are associated with a substantially increased risk of variceal bleed. The reported incidence of LEV ranges from 9% to 49%. In a recent review, Boyer, using a prevalence of LEV of 20%, estimated that a 100 screening endoscopic examinations need to be performed to prevent 1 to 2 cases of variceal bleeding.

It is noteworthy however that variceal hemorrhage is not confined to patients with large esophageal varices although they are more likely to bleed from ruptured varices than patients with small esophageal varices .

Cirrhotic patients frequently undergo screening endoscopy for the presence of esophageal varices (EV). In the future, this social and medical burden will increase due to the greater number of patients with chronic liver disease and their improved survival.

Therefore, the identification of the clinical features that can accurately predict LEV and help identify patients at the greatest risk of bleeding is quite attractive. This could thus make it possible to identify the population with a high probability of LEV that requires confirmation by endoscopy, since the regular use of endoscopy is limited due to cost and discomfort, resulting in poor compliance.

The usual clinical practice is to screen all patients with established cirrhosis at the time of diagnosis by upper endoscopy for the presence of varices. Patients with large varices should be treated with non-selective beta

blockers to reduce the incidence of first variceal bleeding. However, fewer than 50% of cirrhotic patients have varices at screening endoscopy and most have small sized varices, with a low risk of bleeding.

In order to reduce the increasing burden that endoscopy units will have to bear, some studies have attempted to identify characteristics that non-invasively predict the presence of any esophageal varices or of large esophageal varices . These studies have shown that biochemical, clinical, and ultrasonographic parameters alone or together have good predictive power for non-invasively assessing the presence of esophageal varices . Overall, the most common result of these studies was that parameters directly or indirectly linked to portal hypertension, such as splenomegaly and decreased platelet count, were predictors of the presence of esophageal varices .

In a study by Thomopoulos et al (2003) seventeen variables considered relevant to the presence of esophageal varices were tested and they came to the conclusion that Thrombocytopenia, splenomegaly and ascites are independent predictors of large esophageal varices in cirrhotic patients.The authors suggest that endoscopy could be avoided safely in cirrhotic patients with none of these predictive factors, as large varices are absent in this group of patients.

However, in patients with chronic liver disease the presence of decreased platelet count may depend on several factors other than portal hypertension, such as shortened platelet mean lifetime, decreased

thrombopoietin production, or myelotoxic effects of alcohol or hepatitis viruses. On the other hand, the presence of splenomegaly in cirrhotic patients is likely the result of vascular disturbances that are mainly related to portal hypertension. With this in mind, according to Gianni et al(2003) , their study used the platelet count/spleen diameter ratio as a parameter linking thrombocytopenia to spleen size in order to introduce a variable that takes into consideration the decrease in platelet count, which most likely depends on hypersplenism.

According to Gianni et al (2003) use of the platelet count/spleen diameter ratio would have avoided performing unnecessary endoscopies in all patients with a cut off >909 without running the risk of not diagnosing esophageal varices

Analysis of patients with compensated disease was of particular importance. In fact, predicting the presence of esophageal varices in patients with no signs of decompensation could be especially useful and its clinical importance has recently been emphasised.They observed that even among patients with compensated disease, platelet count/spleen diameter ratios were significantly different between those without esophageal varices and those with esophageal varices , and the platelet count/spleen diameter ratio had the highest accuracy for identifying patients with esophageal varices .

Most importantly, this parameter proved to be independent of the Child-Pugh classification allowing a more confident use even in patients with compensated disease.

In many studies Serum ascitic albumin gradient (SAAG) was found to be an independent predictor of portal hypertension and Esophageal varices especially in alcoholic cirrhosis . The serum-ascites albumin (SAA) gradient has been defined as the serum albumin concentration minus the ascitic fluid albumin concentration. The SAA gradient is superior to the exudate-transudate concept to classify ascites, being a exact portal hypertension (PH) marker. An elevated SAA gradient (1.1 g/L or greater) correlates with Portal Hypertension, whereas a low gradient indicates no Portal Hypertension. Thus the SAA gradient correlates well with Portal Hypertension in cirrhotic patients.

To propose that portal hypertension exists by the serum-ascites albumin gradient (SAAG) possesses a validity rate of 96.7% in the adult population.(Demyrel et al 2003).

In several studies recently carried out, it was emphasized that serum-ascites albumin gradient (SAAG) based on the difference between the albumin levels of serum and ascites fluid should be used to determine the etiology of the ascites cases instead of discrimination between transudate and exudate. It was shown that such a classification has a validity rate of 90% or more in detecting the ascites of portal hypertension.

In several studies on cirrhosis due to alcohol, the correlation between SAAG and esophageal varices was emphasized and additionally, SAAG was proposed to be a factor determining the degree of portal hypertension and the prognosis in patients with cirrhosis due to alcohol.There are scant studies in the literature to evaluate SAAG and esophageal varices in the patients with non-alcoholic cirrhosis. When the value of SAAG was more than 2 , strong correlation existed even in Non alcoholic cirrhosis.

AIMS AND OBJECTIVES

1. To identify non invasive parameters for prediction of esophageal varices in newly diagnosed patients with cirrhosis.

2. To assess the Predictive value of Platelet count/ splenic diameter ratio in predicting esophageal varices in cirrhotic patients.

3. To assess the usefulness of SAAG(Serum ascitic albumin gradient) in predicting esophageal varices in patients with cirrhosis.

4. To assess the predictive value of combining two parameters; Platelet count/ splenic diameter ratio and Serum ascitic albumin gradient (SAAG) in patients with decompensated liver disease presenting as ascites.

REVIEW OF LITERATURE

Cirrhosis is a pathologically defined entity that is associated with a spectrum of clinical manifestations.[34]

Definition

Cirrhosis is defined anatomically as a diffuse process with fibrosis and nodule formation. Although the causes are many, the end results are the same.[59]

Evolution of cirrhosis [34]

The cardinal pathological features reflect irreversible chronic injury of the hepatic parenchyma and include extensive fibrosis in association with formation of regenerative nodules. These features result from hepatocyte necrosis, collapse of supporting reticulin network with subsequent connective tissue deposition, distortion of vascular bed, and nodular regeneration of remaining liver parenchyma. The pathologic process should be viewed as a final common pathway of many types of chronic liver injury. Clinical features of cirrhosis derive from the morphological alterations and often reflect the severity of hepatic damage rather than the etiology of the underlying liver disease. Loss of functioning hepatocellular mass may lead to jaundice, edema, coagulopathy, and a variety of metabolic abnormalities; fibrosis and distorted vasculature lead to portal hypertension and its sequelae, including gastro esophageal varices and splenomegaly. Ascites and hepatic encephalopathy result from both hepatocellular insufficiency and portal hypertension.

Classification of cirrhosis[59]

Three anatomical types of cirrhosis are recognized; micro nodular, macro nodular and mixed. Micro nodular cirrhosis is characterized by thick regular septae, by regenerating small nodules varying little in size, and by involvement of every lobule. The macro nodular liver may represent impaired capacity for regrowth as in alcoholism, malnutrition, old age or anemia. Regeneration in a micro nodular cirrhosis results in a macronodular or mixed appearance. With time, micronodular cirrhosis often converts to macronodular.

Aetiology:

1. Alcohol.
2. Viral hepatitis types B ± delta; C..
3. Metabolic, e.g. haemochromatosis, Wilson's disease, α_1 antitrypsin deficiency, type IV glycogenosis, galactosaemia, congenital tyrosinosis and non-alcoholic steatohepatitis.
4. Prolonged cholestasis, intra-and extra-hepatic.
5. Hepatic venous outflow obstruction, e.g. venoocclusive disease, Budd-Chiari syndrome, constrictive pericarditis.
6. Disturbed immunity (autoimmune hepatitis).
7. Toxins and therapeutic agents, e.g. methotrexate, amiodarone.
8. Indian childhood cirrhosis.
9. Cryptogenic cirrhosis.

Diagnosis of cirrhosis

A) Clinical history [34,58,59]

Fatigue and weight loss, loss of libido, anorexia and flatulent dyspepsia, abdominal pain, Jaundice, colour of urine and faeces, swelling of legs or abdomen, hemorrhage - nose, gums, skin, alimentary tract. Past health: jaundice, hepatitis, drugs ingested, blood transfusion. Social: alcohol consumption.

B) Examination:

Nutrition, fever, fetor hepaticus, jaundice, pigmentation, purpura, finger clubbing, white nails, vascular spiders, palmar erythema, gynaecomastia, testicular atrophy, distribution of body hair.

Abdomen: ascites, abdominal wall veins, liver, spleen, edema

Neurological changes: mental functions, stupor, and tremor

C)Investigations :

Haematology

- Hemoglobin
- Leukocyte count
- Platelet count
- Prothrombin time

Serum biochemistry

- Bilirubin
- Transaminases Immunoglobulins
- Alkaline phosphatase
- γ - Glutamyl transpeptidase
- Albumin and globulin

If ascites present

- Serum electrolytes.
- Daily weight.
- Urea and creatinine.
- 24 hours urinary volume and sodium.
- SAAG

Serum immunological investigations

- Hepatitis B Ag, Anti HCV.
- Alpha-fetoprotein.
- Smooth muscle, mitochondrial, nuclear antibodies.

Hepatic CT scan or ultrasound :

Using ultrasound, cirrhosis is suggested by line surface nodularity and portal vein mean flow velocity. The caudate lobe is enlarged relative to the right lobe. Regeneration nodules may be shown as focal lesions. CT scan is cost-effective for the diagnosis of cirrhosis and its complications. Liver size can be assessed and the irregular nodular surface seen. After intravenous contrast, the portal vein and hepatic veins can be identified in the liver, and a collateral circulation with splenomegaly may give confirmation to the diagnosis of portal hypertension. Ascites can be seen.

Liver biopsy :

Biopsy diagnosis of cirrhosis may be difficult. Reticulin and collagen stains are essential for the demonstration of a rim of fibrosis around the nodule.

EEG :EEG is indicated if neuropsychiatric changes are present and to detect early changes in pre-coma.

Compensated cirrhosis [59]

The disease may be discovered at a routine examination or biochemical screen, or at operation undertaken for some other condition. Cirrhosis may be suspected if the patient has mild pyrexia, vascular spiders, palmar erythema, or unexplained epistaxis or edema of the ankles. Firm enlargement of the liver and splenomegaly are helpful diagnostic signs.

Vague morning indigestion and flatulent dyspepsia may be early features in the alcoholic cirrhotic. Confirmation should be sought by biochemical tests, scanning and if necessary, by liver biopsy. Biochemical tests may be quite normal in this group. The most frequent changes are a slight increase in the serum transaminase or γ-GT level. Diagnosis is confirmed by needle liver biopsy.

Decompensated cirrhosis

The patient usually seeks medical advice because of ascites and or jaundice. General health fails with weakness, muscle wasting and weight loss. Continuous mild fever (37.5-38°C) is often due to gram-negative bacteraemia, to continuing hepatic cell necrosis or to liver cell carcinoma. A liver flap may be present. The deeper the jaundice, the greater the liver cell dysfunction.

Pigmentation of the skin and clubbing of the fingers are occasionally seen. Purpura over the arms, shoulders and shins may be associated with a low platelet count. Spontaneous bruising and epistaxis reflect a prothrombin

deficiency. The blood pressure is low. Sparse body hair, vascular spiders, palmar erythema, white nails and gonadal atrophy are common. Ascites and edema of the legs is frequently associated. The liver may be enlarged (early stages), with a regular edge, or contracted and impalpable (late stages). The spleen may be palpable.[59]

Child - Pugh classification [18,34,58,59]

CHILD PUGH CLASSIFICATION			
	A	**B**	**C**
S. Bilirubin	<2.0	2-3	>3
S. Albumin	>3.5	2.8-3.5	<2.8
Ascites	None	Slight or Controlled	Moderate or Uncontrolled
Encephalopathy	None	Minimal	Coma
ProthrombinTime(sec) Or INR	0-4 <1.7	4-6 1.7-2.3	>6 >2.3

The total score classifies patients into grade A (5-7) B(7-9) or C(>10). Poor prognosis is associated with a prolonged prothrombin time, marked ascites, gastrointestinal bleeding, advanced age, high daily alcohol consumption, high serum bilirubin and alkaline phosphatase, low albumin values, and poor nutrition.

Patients with compensated cirrhosis become decompensated at the rate of 10% per year. Ascites is the usual first sign. Decompensated patients have around a 20% 5-year survival.[34,58,59]

According to Madhotra et al(2002) [42] and Zaman et al(2001)[64] the prevalence of esophageal varices in cirrhosis increases with severity of liver disease, as assessed by Child Pugh Classification.

The following points are useful prognostically:

- Liver Size. A large liver carries a better prognosis than a small one because it is likely to contain more functioning cells.
- Hemorrhage from oesophageal varices. If liver function is good, hemorrhage may be tolerated; if poor, hepatic coma and death are probable.
- Persistent hypotension (systolic BP<100 mmHg) is serious.
- Ascites worsens the prognosis.
- If decompensation has followed hemorrhage, infection or alcoholism, the prognosis is better than if it is spontaneous, because the precipitating factor is correctable.
- Jaundice, especially if persistent, is a serious sign
- Neurological complication. The significance of encephalopathy depends on the clinical circumstances. Developing in the course of progressive hepato-cellular failure, it carries a bad prognosis. Chronic

and those with an extensive portal systemic collateral circulation who respond well to medical treatment carry good prognosis.

- Biochemical tests. If the serum albumin is less than 25g/L the outlook is poor. Hyponatraemia (serum sodium<120mmol/L), if unrelated to diuretic therapy, is grave. Serum transaminase and globulin levels give no guide to prognosis.
- Alcoholic cirrhotics, if they abstain, respond better than those with 'cryptogenic' cirrhosis
- The response to therapy. If the patient has failed to improve within 1 month of starting hospital treatment, the outlook is poor.
- Hepatic histological changes. Sections are useful in evaluating the extent of necrosis and of inflammatory infiltration. A fatty liver responds well to treatment.

PORTAL HYPERTENSION

ANATOMY OF PORTAL VENOUS SYSTEM[59]

Portal system includes all veins that carry blood from the alimentary tract, the spleen, pancreas and gall bladder. Portal vein is formed by union of superior mesenteric vein and splenic vein just posterior to the head of pancreas and it enters the liver at the porta hepatis and it divides into two main branches, one to each lobe. Portal blood flow in man is 1000-1200mL/min. Portal pressure is about 5-10 mm Hg.

COLLATERALS

Abdominal wall veins

Prominent collateral veins radiating from umbilicus are termed caput medusae. This is rare and usually only one or two veins, frequently epigastric, are seen. The blood flows away from umbilicus.

VARICES

Esophageal:

The major blood supply to oesophageal varices is the left gastric vein. The posterior branch usually drains into the azygos stem, whereas the anterior branch communicates with varices just below the oesophageal junction and forms a bundle of thin parallel veins that run in the junction area and continues in large tortuous veins in the lower esophagus. Intraepithelial veins may correlate with red spots seen on endoscopy and predict variceal rupture. The superficial venous plexus drains into larger, deep intrinsic veins. Perforating veins connect the deeper veins with the fourth layer of adventitial plexus. Typical large varices arise from the main trunks of deep intrinsic veins and these communicate with gastric varices.

Gastric

These are largely supplied by short gastric veins and drain into the deep intrinsic veins of oesophagus. They are particularly prominent in patients with extra hepatic portal hypertension.

Colo - rectal

These develop secondary to inferior mesenteric - internal iliac venous collaterals. They are visualized by colonoscopy. Collaterals between the superior haemorrhoidal (portal) veins and the middle and inferior haemorrhoidal (systemic) veins lead to anorectal varices.

Portal hypertensive gastropathy

This is almost always associated with cirrhosis and is seen in the fundus and body of the stomach. Histology shows vascular ectasia in mucosa. These gastric changes may be increased after sclerotherapy.

HAEMODYNAMICS OF PORTAL HYPERTENSION

The fundamental haemodynamic abnormality is an increased resistance to portal flow. This may be mechanical due to the disturbed architecture and nodularity of cirrhosis or due to obstructed portal vein.. Splanchnic vasodilatation is probably the most important factor in maintaining the hyper dynamic circulation. The increased portal flow raises the oesophageal variceal transmural pressure. There seems to be interplay of vasodilators and vasoconstrictors. These might be formed by the hepatocyte, fail to be inactivated by it or be of gut origin and pass through intrahepatic or extrahepatic venous shunt.

CLASSIFICATION AND CAUSES OF PORTAL HYPERTENSION [58]

I) Primary increased flow

1.Arterioportal venous fistula. 2 Splenic capillary hemangiomatosis.

II) Primary increased resistance

1. Prehepatic: 1.Thrombosis/ cavernous transformation of the portal vein 2.Splenic vein thrombosis.

2. Intrahepatic :1.)Presinusoidal – Schistosomiasis, Sarcoidosis, Myeloproliferative diseases/ myelofibrosis, Congenital hepatic fibrosis, Idiopathic portal hypertension, Chronic arsenic hepatotoxicity, Vinyl chloride hepatotoxicity,Early primary biliary cirrhosis, Early primary sclerosing cholangitis. 2) Sinusoidal / mixed – cirrhosis secondary to chronic hepatitis, Cryptogenic cirrhosis, Methotrexate, Alcoholic hepatitis, Hypervitaminosis A, Incomplete septal fibrosis, Nodular regenerative hyperplasia. 3) Post sinusoidal – Veno-occlusive disease, Hepatic vein thrombosis(Budd-Chiari syndrome). 4) Post hepatic – Inferior venacaval web, Constrictive pericarditis, Tricuspid insufficiency, severe right heart failure.

CLINICAL FEATURES OF PORTAL HYPERTENSION[18,34,58,59]

History a.) alcoholism b) jaundice c) melena d) hematemesis

General examination.

Stigmata of liver disease: The stigmata of cirrhosis include vascular spiders, palmar erythema, anemia, and ascites. Precoma should be excluded.

Other features: hepatomegaly, venous hums, abdominal wall veins

Spleen :

The spleen (firm) enlarges progressively. It may be mild to moderate in size. Size bears little relation to the portal pressure. An enlarged spleen is the single most important diagnostic sign of portal hypertension. Massive splenomegaly is associated with pancytopenia. (secondary hypersplenism).

Ascites:

The portal hypertension raises the capillary filtration pressure, and determines fluid localization to the peritoneal cavity. Ascites in cirrhosis always indicates liver cell failure in addition to portal hypertension. In cirrhosis, the serum albumin concentration is usually at least 1gm/dL higher than that of the ascitic fluid, thus resulting in a high serum - ascites albumin gradient >/=l.l gm/dL reflecting indirectly the abnormally high hydrostatic pressure gradient between the portal bed and the ascitic compartment. Conversely presence of a low SAAG (< 1.1 gm/dl) will usually exclude cirrhosis and portal hypertension.

INVESTIGATIONS

Endoscopy

The size of varix must be graded [59]

- Grade 1 (Fl): the varices can be depressed by the endoscope
- Grade 2 (F2): the varices cannot be depressed by the endoscope
- Grade 3 (F3) the varices are confluent around the circumference of the oesophagus.

CONN'S GRADING [59]

- Grade I - small varices detectable on valsalva only
- Grade II -1-3 mm varix- in both phases of respiration
- Grade III - 3-6 mm varices, not occluding the lumen
- Grade IV - >6mm varices, occluding the lumen

Larger the varix, the chances of bleeding is more. Varices usually appear white and opaque. Dilated sub epithelial veins may appear as raised cherry red spots and red whale markings. The haemocystic spot is approximately 4mm in diameter. It represents blood coming from deeper extrinsic veins of oesophagus straight out towards the lumen through a communicating vein into the more superficial submucosal veins. Red colour

is usually associated with larger varices. All these colour changes and particularly the red colour sign predict variceal bleeding. Portal hypertensive gastropathy is seen largely in the fundus. It is seen as a mosaic like pattern. Variceal (azygos) blood flow can be assessed during diagnostic endoscopy by a Doppler US probe passed down the biopsy channel of the standard gastroscopy.

Imaging the portal venous system[18,34,58,59]

Ultrasound:

A large portal vein suggests portal hypertension. If collaterals are seen, this confirms portal hypertension.

Doppler ultrasound

Doppler US demonstrates the anatomy of the portal veins and hepatic artery. Doppler US shows spontaneous hepato-fugal flow in portal, splenic and superior mesenteric veins in patients with cirrhosis. Variceal bleeding is more likely if the flow is hepatopetal. Colour Doppler is a good way of demonstrating portal systemic shunts and the direction of flow in them.

Duplex Doppler has-been used to measure portal blood flow. In cirrhosis, the portal vein velocity tends to fall and when less than 6cm/s portal hypertension is likely.

C.T scan

After contrast, portal vein patency can be established and esophageal varices may be shown as intraluminal protrusions enhancing after contrast. Gastric varices show as rounded structures, indistinguishable from the gastric wall.

In cirrhosis, the venogram varies widely. It may be completely normal or may show filling of large numbers of collateral vessels with gross distortion of the intra-hepatic pattern ('tree in winter appearance).

Portal pressure measurement

A balloon catheter is introduced into the femoral vein and, under fluoroscopic control, into the hepatic vein. Measurements taken in the wedged hepatic venous pressure (WHVP) and free hepatic venous pressure (FHVP) positions by inflating and deflating the balloon in the tip of the catheter. The hepatic venous pressure gradient (HVPG) is the difference between WHVP and FHVP. This is the portal (sinusoidal) venous pressure. The normal HVPG is 5-6 mm Hg and values of about 20mmHg are found in patients with cirrhosis. HVPG may relate to survival and also to prognosis in patients with bleeding oesophageal varices. Its value in the prediction of variceal bleeding is uncertain.[34,59]

Variceal pressure:

An endoscopic pressure gauge may be fixed to the end of the endoscope. The level of venous pressure is a major factor predicting variceal hemorrhage.

BLEEDING OESOPHAGEAL VARICES [59]

Predicting rupture

Sixty five per cent of cirrhotic patients with varices will not bleed within 2 years of diagnosis, but 50% will die of the first hemorrhage. There is a strong correlation between variceal size assessed endoscopically, and the probability of bleeding. Intravariceal pressure is less important, although a portal pressure above 12 mmHg appears necessary for varices to form and subsequently bleed. 'Red spots', danger signs seen at endoscopy, are valuable indictors of imminent hemorrhage. Child's grade is used to assess hepato-cellular function. It is the most important predictor of the likelihood of bleeding. It correlates with variceal size, with the presence of endoscopic red signs and with the response to treatment.

These three variables - size, presence of red signs and hepatocellular function-are the best predictors of bleeding. Patients with alcoholic cirrhosis may be at the most risk. Doppler sonography predicts the likelihood of bleeding. This is based on velocity and diameter of the portal vein, spleen size and the presence of collaterals.

Prevention of bleeding

Liver function must be improved, for instance, by abstaining from alcohol. Aspirin and NSAIDs should be avoided. Propranolol is a non-selective β-blocker, which reduces portal pressure by splanchnic vaso-constriction and, to a lesser extent, by reducing cardiac output. The drug is given in a dose, which reduces the resting pulse rate by 25% 12h after intake. The portal pressure must be maintained at 12mm Hg or lower. Propranolol is recommended for those with large varices and with red endoscopic danger signs. Patients with an HVPG greater than 12mmHg should be treated whatever the size of the varices. Nadolol gives equivalent results. Isosorbide-5 mononitrate is equally effective in prophylaxis of the first bleed, but the probability of death is significantly greater, particularly in those more than 50 years old. The addition of nitrate to β-blocker should be reserved for those failing therapy with the β-blocker alone. Variceal sclerotherapy or ligation is not so satisfactory or cost effective as vaso-active active drugs.

Diagnosis of bleeding

The clinical features are those of gastro intestinal bleeding with the added picture of portal hypertension. Endoscopy is performed routinely to confirm the source of the bleeding.

Prognosis[59]

Between 30 and 50% will die within 6 weeks of the first bleed. The prognosis is determined by the severity of the hepato-cellular disease. The

ominous triad of jaundice, ascites and encephalopathy is associated with 80% mortality. The 1-year survival in good-risk (Child grade A and B) patients is about 85% and in bad - risk (Child grade C) patients about 30%. Alcoholics have a worse prognosis, as hepatocellular disease is greater. Abstinence from alcohol considerably improves the prognosis. A low portal blood velocity by Doppler predicts shorter survival.

As liver biopsy is invasive there has been a lot of interest in the ability to detect cirrhosis by non invasive means, such as sonography.

THE SONOGRAPHIC PATTERNS ASSOCIATED WITH CIRRHOSIS [34,59]

- Volume redistribution Several studies have evaluated the ratio of the caudate lobe width to the right lobe width (C/RL) as an indicator of cirrhosis. A C/RL value of 0.65 is considered indicative of cirrhosis.
- Coarse echotexture

  Increased echogenicity and coarse echotexture are frequent observations in diffuse liver disease
- Nodular surface

The nodularity corresponds to the presence of regenerating nodules and fibrosis.

- Regenerating nodules

Regenerating nodulesrepresent regenerating hepatocytes surrounded by a fibrotic septa.

- Dysplastic nodules

Dysplastic nodules or adenomatous hyperplastic nodules are larger than regenerating nodules (diameter ≥ 10 mm) and are considered premalignant.

DOPPLER CHARACTERISTICS OF CIRRHOSIS[58,59]

The normal Doppler wave form of the hepatic veins reflects the hemodynamics of the right atrium. The waveform is triphasic: two large antegradediastolic and systolic waves and a small retrograde wave corresponding to the atrial "kick". Because the walls of the hepatic veins are thin, disease of the hepatic parenchyma may alter their compliance. In many patients with compensated cirrhosis (no portal hypertension), the Doppler waveform is abnormal. Two abnormal patterns have been described; decreased amplitude of phasic alterations with reversal of flow; and a flattened waveform. These abnormal patterns have also been found in patients with fatty infiltration of their livers.

As cirrhosis progresses, luminal narrowing of the hepatic veins may be associated with flow alterations visible on colour and spectral Doppler. High velocity signals through an area of narrowing produce colour aliasing and turbulence.

The hepatic artery waveform also shows altered flow dynamics in cirrhosis and chronic liver disease. The vasoconstriction of the hepatic artery occurs as a normal response to the increased portal venous flow stimulated by eating (≥ 20%). In patients with cirrhosis and chronic liver disease, the normal increase in postprandial resistive index is blunted.

SONOGRAPHIC FINDINGS IN PORTAL HYPERTENSION

They include the secondary signs of splenomegaly, ascites and portosystemic venous collaterals. When the resistance to blood flow in the portal vein exceeds the resistance to flow in small communicating channels between the portal and systemic circulations, portosystemic collaterals form. Thus although the caliber of portal vein may initially be increased (≥ 1.3 cm) in portal hypertension, with the development of portosystemic shunts, the portal vein caliber will decrease in size. Five major sites of collaterals are visualized by ultrasound.

- Gastroesophageal junction – Between the coronary and short gastric veins and the systemic esophageal veins. Dilatation of coronary veins (0.7) is associated with severe portal hypertension (portohepatic gradient >10 mm Hg).

- Paraumbilical vein – Runs in the falciform ligament and connects the left portal vein to the systemic epigastric veins near the umbilicus (Cruveilhier – Baumgarten syndrome). Several authors have suggested that, if the hepatofugal flow in the patent paraumbilical vein

exceeds the hepatopetal flow in the portal vein, patients may be protected from developing esophageal varices.

- Splenorenal and gastro renal – Tortuous veins may be seen in the region of the splenic and left renal hilus, which represent collaterals between splenic, coronary and short gastric veins and the left adrenal or renal veins.

- Intestinal – Regions in which the gastrointestinal tract becomes retroperitoneal so that the veins of the ascending and descending colon, duodenum, pancreas and liver may anastomose with the renal, phrenic and lumbar veins.

- Hemorrhoidal – The perianal region were the superior rectal veins, which extend from the inferior mesenteric vein, anastomose with the systemic middle and inferior rectal veins.

Duplex doler sonography provides additional information regarding direction of portal flow. False results may occur, however when sampling is obtained from periportal collaterals in patients with portal vein thrombosis or hepatofugal portal flow. Normal portal venous flow rates will vary in the same individual, increasing postprandially and during inspiration and decreasing following exercise or when the patient is in upright position. An increase of less than 20% in in the diameter of the portal vein with

deepinspiration indicates portal hypertension with 81% sensitivity and 100% specificity.

The normal portal vein demonstrates an undulating hepatopetal flow. Mean portal flow velocity is approximately 15 to18 cm/sec and varies with respiration and cardiac pulsation. As portal hypertension develops the flow in the portal vein loses its undulatory pattern and becomes monophasic. As the severity of the portal hypertension increases, flow becomes biphasic and finally hepatofugal. Intravenous arterial – portal venous shunting may also be seen.

Chronic liver disease is also associated with increases splanchnic blood flow. Recent evidence suggest that portal hypertension is in part caused by the hyperdynamic flow state of cirrhosis.[36]

The limitations of Doppler sonography in the evaluation of portal hypertension include the ability to accurately determine vascular pressure and flow rates. Patients with portal hypertension are often ill with contracted livers, abundant ascites and floating bowel, all of which are a technical challenge. On comparing duplex Doppler with MR angiography, MR imaging was superior in the assessment of patency of the portal vein and surgical shunts as well as in detection of varices. However when the Doppler is technically adequate, it was accurate in the assessment of normal portal anatomy and flow direction. Duplex doppler sonography has the added

advantages of decreased cost and portability of the equipment and therefore should be used as an initial screening method for portal hypertension.

NON INVASIVE PARAMETERS FOR PREDICTION OF ESOPHAGEAL VARICES

Studies have attempted to identify characteristics that non-invasively predict the presence of any esophageal varices or of large esophageal varices.[7,12,22,24,26,27,28,3642,46,47,50] These studies have shown that biochemical, clinical, and ultrasonographic parameters alone or together have good predictive power for non-invasively assessing the presence of esophageal varices. .Overall, the most common result of these studies was that parameters directly or indirectly linked to portal hypertension, such as splenomegaly and decreased platelet count, were predictors of the presence of esophageal varices[26,56,60,64,65]

In a study by Thomopolos et al (2003)[60] seventeen variables considered relevant to the presence of esophageal varices were tested and they came to the conclusion that Thrombocytopenia, splenomegaly and ascites are independent predictors of large esophageal varices in cirrhotic patients.

In a study performed by Hoefs et al(1983)[35], it was shown that an excellent correlation exists between portal hypertension and Serum- ascitic albumin gradient (SAAG).

CHRONIC LIVER DISEASE AND PLATELET COUNT

Abnormalities in platelet count and function are common in patients with all forms of liver disease. In patients with chronic liver disease and portal hypertension, a low platelet count is due in part to increased splenic sequestration and to low thrombopoietin levels, the key regulator of platelet function produced mainly by liver. Decreased production of platelets from the bone marrow follows alcohol excess, folic acid deficiency and viral hepatitis.

Platelet function, in particular aggregation, is impaired in patients with cirrhosis, particularly Child's grade C, due to an intrinsic defect and circulating serum factors. There is reduced availability of arachidonic acid for prostaglandin production, and also a reduction in platelet adenosine triphosphate and 5-hydroxytryptamine. Abnormal platelet aggregation due to disseminated intravascular coagulation may be an additional important factor in severe liver failure.

The thrombocytopenia of chronic liver disease (usually 60-90 X 10^9/L) is extremely frequent and is largely due to hypersplenism.[23,26,34,49,58,59]

Several studies have assessed the role of platelet count in predicting esophageal varices.

According to Pilette et al (1999)[50] in patients with cirrhosis, the diagnostic accuracy of platelet count (<1,60,000) for large varices provided a sensitivity of 80% and a specificity of 58% and a platelet count of ≥2,60,000 has a negative predictive value of ≥ 91%.

According to Schepis et al(2001).[57] a platelet count less than 100 x 10^9/L was found to be having a role in predicting esophageal varices .

Platelet count of < 68000/cubic mm had a specificity of 73% in predicting esophageal varices as reported by Madhotra et al.(2002)[42]

Zaman et al (1999) found that a platelet count of 90 x 10^3/μL or less had a role in predicting varices. [65]

Study by Ng et al(1999) reported that the optimal critical value for the platelet count was 150 x 10^9/L, of patients without thrombocytopenia and ascites. [46]

SPLENOMEGALY

According to study by Chalasani et al.(1999)[7] splenomegaly and low platelet count were independent predictors of large esophageal varices. On the basis of these variables, cirrhotics were stratified into high risk groups for the presence of large esophageal varices. Patients with platelet count of ≥ 88,000/cu mm and no splenomegaly by physical examination had a risk of large esophageal varices of 7.2%. Those with splenomegaly or platelet count < 88,000/cu mm had a risk of large esophageal varices . Their data showed that clinical predictors could be used to stratify cirrhotic patients for the risk of rupture of large esophageal varices and such stratification could be used to improve the cost effectiveness of screening endoscopy.

Thomopolos et al(2003) have reported splenomegaly as an independent predictor of esophageal varices in cirrhotic patients.[60]

Torres et al (1996) investigated the association and correlation between ultrasonographic parameters of portal hypertension and the presence and level of portal hypertension (determinate by the serum-to-ascites albumin concentration gradient). They demonstrated that ultrasonographic splenomegaly studied by longitudinal diameter of the spleen discriminate patients with portal hypertension with a high positive predictive value (94.4%), although it didn't happen with transverse diameter of the spleen.[63]

According to Chalasani et al (1999) .[7] splenomegaly detected by computed tomographic scan (odds ratio: 4.3; 95% confidence interval: 1.6-11.5) or by physical examination (odds ratio: 2.0; 95% confidence interval: 1.1-3.8), and low platelet count were independent predictors of large esophageal varices. On the basis of these variables, cirrhotics were stratified into high- and low-risk groups for the presence of large esophageal varices. Patients with a platelet count of > or = 88,000/mm3 (median value) and no splenomegaly by physical examination had a risk of large esophageal varices of 7.2%. Those with splenomegaly or platelet count < 88,000/mm3 had a risk of large esophageal varices of 28% ($p < 0.0001$). The authors conclude that clinical predictors could be used to stratify cirrhotic patients for the risk of large esophageal varices.

According to Sanjay Kumar Sharma et al (2006) .[56] presence of palpable spleen and low platelet count are independent predictors of presence of large esophageal varices in patients with cirrhosis. Use of these parameters

may help identify patients with a low probability of large esophageal varices who may not need endoscopy. This may help reduce costs and discomfort for these patients and the burden on endoscopy units.

RELEVANCE OF PLATELET COUNT/SPLENIC DIAMETER RATIO

Gianni et al(2003)[26] proposed platelet count/ splenic diameter ratio as a non invasive marker for predicting esophageal varices in patients with liver cirrhosis. Parameters directly or indirectly linked to portal hypertension, such as splenomegaly and decreased platelet count, were predictors of the presence of esophageal varices . However, in patients with chronic liver disease the presence of decreased platelet count may depend on several factors other than portal hypertension, such as shortened platelet mean lifetime, decreased thrombopoietin production, or myelotoxic effects of alcohol or hepatitis viruses. On the other hand, the presence of splenomegaly in cirrhotic patients is likely the result of vascular disturbances that are mainly related to portal hypertension. With this in mind, the study used the platelet count/spleen diameter ratio as a parameter linking thrombocytopenia to spleen size in order to introduce a variable that takes into consideration the decrease in platelet count which most likely depends on hypersplenism caused by portal hypertension.

In the study Maximum spleen bipolar diameter was estimated by means of ultrasound scan and was expressed in millimetres (mm). Platelet

count/spleen diameter ratio of all patients was calculated. They found that Spleen diameter was higher while platelet count/spleen diameter ratio was lower in patients with esophageal varices . Receiver operating characteristic curve (ROC curves) were used to assess the platelet count/spleen diameter ratio cut off with the best sensitivity and specificity for a diagnosis of esophageal varices (cut off=909, sensitivity=100% (95% CI 100–100); specificity=93% (95% CI 82–98)) . The prevalence adjusted positive and negative predictive values for a platelet count/spleen diameter ratio ≤909 were 96% and 100%, respectively. Moreover, accuracy of this platelet count/spleen diameter ratio cut off as evaluated by the *c* index was 0.981 (95% CI 0.943–0.996). Both spleen diameter and platelet count cut offs with the best sensitivity and specificity for a diagnosis of esophageal varices that were identified by means of ROC curves had prevalence adjusted positive and negative predictive values and accuracies that were lower than those of the platelet count/spleen diameter ratio.

Gianni et al (2003)[26] report that the use of this ratio is of interest and is not redundant, and this hypothesis is supported by a number of both clinical and statistical reasons. Firstly, from a clinical point of view, platelet count may decrease for several reasons in patients with chronic liver disease.

Thus the use of platelet count alone as a non-invasive predictor of esophageal varices can be misleading and cannot be solely attributed to portal hypertension. Indeed, the use of the platelet count/spleen diameter ratio

bypasses this possible drawback since it "normalizes" platelet count to splenic sequestration, most likely representing the aliquot of thrombocytopenia caused by portal hypertension. Secondly, from a statistical point of view, the platelet count/spleen diameter ratio was the only parameter independently associated with the presence of esophageal varices that was selected by a multivariate analysis which also included the single parameters.

The study showed that the use of the platelet count/spleen diameter ratio would have avoided performing unnecessary endoscopies in all patients with a cut off >909 without running the risk of not diagnosing esophageal varices. As far as cost benefit analysis is concerned, applying the "platelet count/spleen diameter ratio strategy" would lower the cost of esophageal varices screening in patients with cirrhosis.

ASCITES [59]

Ascites is defined as presence of free fluid within the peritoneal cavity. Cirrhosis is one of the commonest causes of ascites.The abnormalities associated with formation of ascites in patients with cirrhosis are Portal Hypertension, renal retention of sodium, splanchanic arterial vasodilatation, systemic vascular changes , increased splanchnic and hepatic lymph formation, hypoalbuminaemia.

Ascites may appear suddenly when hepatocellular function is reduced, for instance by hemorrhage, shock, infection of an alcoholic debauch. This might be related to fall in serum albumin values and or intravascular fluid

depletion. Occlusion of the portal vein may precipitate ascites in a patient with a low albumin level. If the serum albumin minus ascites albumin gradient is greater than 1.1g/dl, it is suggestive of portal hypertension.

Thomopolos et al(2003)[60] found out that ascites along with two other parameters (thrombocytopenia and splenomegaly) was an independent predictor of large esophageal varices in patients with cirrhosis.

The utility of differentiating ascites into 'transudate' and 'exudate' has recently been challenged.

Akriviadis et al(1996)[1]compared the diagnostic accuracy of the serum/ascites albumin gradient, proposed as a new biochemical criterion for the differential diagnosis of ascites, with the markers traditionally used for the classification of peritoneal fluid into transudate and exudates. They concluded that the classification of ascites into transudate and exudate appears to be based on markers with low diagnostic accuracy. Differential diagnosis of ascites should be based on the serum/ascites albumin gradient, which is a reliable marker distinguishing ascites related to portal hypertension from all other causes of ascitic fluid collection, regardless of the presence of bacterial infection.

According to Goyal et al (1989)[29] Serum ascites albumin gradient, showed a strong correlation to portal pressure (r, + 0.83 + 0.88), and was found to be the best diagnostic index (with an overall accuracy of 97 per cent) in distinguishing the 'transudative' from 'exudative' ascites.

Pare et al (1983)[48] Compared serum-ascites albumin concentration gradient, a parameter of oncotic pressure gradient reflecting presence or absence of portal hypertension, with the usual parameters of ascitic fluid analysis in the differential diagnosis of ascites.Authors conclude that the serum-ascites albumin gradient offers the best diagnostic discrimination between ascites caused by liver disease and ascites caused by a neoplasm.

SERUM ASCITES ALBUMIN CONCENTRATION GRADIENT (SAAG)

The serum-ascites albumin (SAA) gradient has been defined as the serum albumin concentration minus the ascitic fluid albumin concentration.[34,59] The SAA gradient is superior to the exudate - transudate concept to classify ascites, being a exact portal hypertension (PH) marker. An elevated SAA gradient (1.1 g/L or greater) correlates with PH, whereas a low gradient indicates no PH. The SAA gradient correlates well with PH in cirrhotic patients.[2,34,59]

Zhu et al (2003)[67] evaluated the diagnostic value and efficacy of the serum-ascites albumin gradient (SAAG). SAAG demonstrates that patients with ascites fluid possess the basis of portal hypertension. SAAG classification can be considered to be a novel standard in ascites fluid analysis.

Dittrich et al (2001)[19] found that there was a significant correlation between the serum-ascites albumin gradient and the hepatic venous pressure

gradient (r = 0.502), indicating the reliability of the serum-ascites albumin gradient in demonstrating the presence of portal hypertension and its relationship with the origin of ascites.

Torres et al (1996)[62] investigated the association between the high serum-to-ascites albumin concentration gradient with the degree and development of oesophageal varices, studied by endoscopy. They also studied its relationship with the degree of impairment of liver function, determined by the Child-Pugh's score.

The study found that the degree of high gradient of albumin could discriminate patients with oesophageal varices finding like a signal of its presence a value of high SAAG greater than 1.435 +/- 0.015 g/dl. It is here demonstrated that the degree of high SAAG does not have any relationship with the degree of impairment of liver function (Child-Pugh's score), prothrombin time, serum bilirubin, degree of encephalopathy neither grade of ascites.

Gurubacharya et al (2005)[32] studied the correlation between the level of serum-ascites albumin concentration gradient (SAAG) and the complications of portal hypertension.

In patients with ascites the presence of esophageal varices is associated only with patients with High SAAG. The presence of esophageal varices in patients with ascites and High SAAG is directly related to the

degree of SAAG. The size of the esophageal varices in patients with ascites and High SAAG is not associated with the degree of SAAG.

Torres et al (1998)[61] found that in patients with ascites the presence of esophageal varices is associated only with patients with High SAAG. The presence of esophageal varices in patients with ascites and High SAAG is directly related to the degree of SAAG. The size of esophageal varices in patients with ascites and High SAAG is not associated with the degree of SAAG. A SAAG value of > or =1.435 +/- 0.015 g/dl is a useful means to predict the presence of esophageal varices in patients with ascites. Finally, in patients with ascites, esophageal varices were more prevalent in those with alcoholic liver disease.

Several studies recently carried out, it was emphasized that serum-ascites albumin gradient (SAAG) based on the difference between the albumin levels of serum and ascites fluid should be used to determine the etiology of the ascites cases instead of discrimination between transudate and exudate. It was shown that such a classification has a validity rate of 90% or more in detecting the ascites of portal hypertension. In several studies on cirrhosis due to alcohol, the correlation between SAAG and esophageal varices was emphasized and additionally, SAAG was proposed to be a factor determining the degree of portal hypertension and the prognosis of the patients in cirrhosis due to alcohol.

In a study performed by Hoefs et al. (1983)[35], it was shown that an excellent correlation exists between portal hypertension and SAAG . In this study, a numeric formula was established for the first time between portal hypertension and SAAG.While it was established in this formula that $p<0.05$ and $r=0.73$, the numeric formula was as follows: Portal gradient=7.08 x [SAAG+3.62]. A similar correlation was found by Rector et al.(1984)[52] . In this study on patients with alcoholic cirrhosis, the correlation between portal hypertension and SAAG was $p=0.001$ and $r= 0.8$. In 1990, Kajani et al.[40] investigated the correlation in patients with alcoholic cirrhosis and with cirrhosis due to other causes separately . In this study, a correlation was found between SAAG and either portal pressure ($r=0.62$) or esophageal varices ($r=0.53$) in alcoholic patients.

But in the patients with non-alcoholic cirrhosis, no correlation was found between SAAG and portal pressure($r=0.39$), while the correlation between SAAG and the varix degree was found to be weaker ($r=0.02$). Although the studies performed on children yielded some common properties, there are remarkable differences between the results of the studies performed on adults versus children. In a study performed by Das et al(2001)[8] on 26 pediatric patients with cirrhosis with primarily unknown etiologies, SAAG was found to be greater than 1.1 in 22 (84%) of the patients, and less than 1.1 in the remaining four (16%) patients. While 20 (91%) of the patients with SAAG values greater than 1.1 had esophageal varices, 50% of the patients

with SAAG values less than 1.1 had varices. Although SAAG in this study was found to have a low specificity and sensitivity, it appeared to be a highly reliable guide for esophageal varices.

In a recent study by Torres et al.(1998)[61], the correlation between SAAG and esophageal varices was studied. In this study, 14 patients with alcoholic cirrhosis were compared by their endoscopic findings and esophageal varices were determined in all of the patients with alcoholic cirrhosis. A correlation was shown between SAAG and esophageal varices in this study (p=0.001)

Demyrel et al (2003)[17] study supports the observation that SAAG values increase in ascites due to portal hypertension. But it supports neither the presence nor the severity of the esophageal varices, which is another important finding of portal hypertension with a close correlation. It was remarkable that esophageal varices were present in all of the patients with an SAAG value greater than 2.0. Tores et al.(1998)[61] observed this in their own data. There was a correlation in study by Demyrel et al (2003)[17] only between the degree of the esophageal varices and ascites level of albumin (p=0.03), but the correlation co-efficient was found to be low (r=0.30). The fact that most of the patients reported in the literature are those patients with cirrhosis due to alcohol makes it difficult to interpret the results on this matter. Although their data showed no linear correlation between SAAG and esophageal varices, it is noteworthy that 90% of the patients with non-

alcoholic cirrhosis presenting with ascites and all of the patients with an SAAG value greater than 2.0 had esophageal varices.

MATERIALS AND METHODS

Type of Study: Cross sectional study.

Sample: Liver clinic, Gastroenterology Department, and Medicine Out Patient Department and In patient wards of Stanley Medical College, Chennai.

Duration of study: 2005 August - 2006 July.

INCLUSION CRITERIA

All newly diagnosed cases of cirrhosis liver, based on physical examination, biochemical parameters, ultrasound abdomen and upper GI endoscopy.

EXCLUSION CRITERIA

- Present or previous history of portal hypertensive bleeding
- Patients with hepatocellular carcinoma
- Portal vein thrombosis
- Previous or current treatment with β blockers, diuretics or other vasoactive drugs.
- Budd Chiari Syndrome.

INVESTIGATIONS DONE

- Complete Hemogram

Hemoglobin (g/dL)	MCV (fL)
Total Count (cells/cmm)	MCHC (g/dL)
Differential Count	PCV
RBC (millions/cmm)	Clotting Time

Platelets (lakhs/cmm) Bleeding Time

- Liver Function Tests

Serum Bilirubin Aspartate Amino Transferase

Serum Albumin Alanine Amino Transferase

Prothrombin Time Alkaline Phosphatase

- Child Pugh Score

Graded into Class A B or C

- Ascitic Fluid Analysis

Colour Protein

Total Cell Count Differential count

Sugar SAAG

- Ultrasound Abdomen

Liver Surface Nodularity Portal Vein Size

Architecture of the liver Splenic vein size

Size of the liver Spleen bipolar diameter

Presence of ascites Collateral circulation

- Upper Gastrointestinal Endoscopy

Presence of esophageal and gastric varices and grading according to Conns grading for esophageal varices .

Portal Hypertensive Gastropathy

Erosions

Red Signs

PROCEDURE

Hundred patients with cirrhosis liver, attending the medical and gastroenterology wards and out patient departments of Stanley Medical College, Chennai , between the months of August 2005 to July 2006 were selected, based on inclusion and exclusion criteria.

All patients in the study underwent a full clinical evaluation .Clinical history and physical examination findings were recorded with particular attention to present or previous hematemesis, malena, bleeding per rectum, bleeding tendencies, alcoholism, blood transfusion, intake of hepatotoxic drugs, exposure to Sexually transmitted diseases, IV drug abuse, jaundice, anemia, edema, stigmata of chronic liver disease, dilated abdominal veins, ascites, splenomegaly and encephalopathy.

All patients underwent biochemical tests, like liver function tests, complete blood counts, renal function tests, prothrombin time, ultrasonography of the abdomen to confirm the presence of cirrhosis and to record the spleen bipolar diameter, portal vein size, ascites and presence of collaterals and Ascitic fluid analysis in patients with ascites. Upper GI endoscopy was done in all patients to confirm the presence of varices and also to grade them.

Data were collected in a predetermined proforma and results were analyzed using Software Statistical package student version 14.0.Continuous variables were analyzed using t-test and categorical variables by Chi square test. Pearson Correlation was used to find correlation between two variables. Receiver operating characteristic curve was used to find the SAAG value with best sensitivity and specificity for predicting esophageal varices .

RESULTS

TABLE 1 : RELATIONSHIP BETWEEN AGE OF THE STUDY POPULATION AND GRADE OF VARICES

Varices		age group						Total
		<20	21-30	31-40	41-50	51-60	>60	
Grade of varices	I	0	0	3	4	2	2	11
	II	3	6	9	5	7	2	32
	III	2	2	5	12	2	2	25
	IV	0	1	3	6	1	1	12
	0	2	2	7	6	2	1	20
Total		7	11	27	33	14	8	100

$\chi 2 = 16.63$ P=0.67 NS

Distribution of grade of varices was studied in various age groups and no significant correlation was detected.

Mean age of the patients in the study was 41.85. SD = 12.72

TABLE 2 : DISTRIBUTION BASED ON SEX

Varices		Sex		Total
		Male	Female	
Grade of Varices	I	4	7	11
	II	19	13	32
	III	17	8	25
	IV	6	6	12
	0	14	6	20
Total		60	40	100

$\chi 2 = 4.56$ P=0.34 NS

No significant gender difference in the distribution of grade of varices was found in our study.

TABLE 3 : DISTRIBUTION BASED ON GRADE OF VARICES

Varices		Frequency	Percent
Grade of Varices	I	11	11.0
	II	32	32.0
	III	25	25.0
	IV	12	12.0
	0	20	20.0
	Total	100	100.0

Based on Conn's Grading, the grading of the varices in study population was done. Grade II varices predominated (32 %). Varices were absent(Grade 0) in 20 % of the patients.

TABLE 4 : RELATIONSHIP BETWEEN HEPATIC ENCEPHALOPATHY AND VARICES

Varices		Hepatic Encephalopathy		Total
		yes	no	
Grade of Varices	I	1	10	11
	II	2	30	32
	III	4	21	25
	IV	3	9	12
	0	0	20	20
Total		10	90	100

$\chi 2 = 6.70$ $P=0.15$ NS

No significant relation between presence of hepatic encephalopathy and grade of varices was found.

TABLE 5 :RELATIONSHIP BETWEEN CHILD PUGH GRADE AND VARICES

Varices		CP grade			Total
		1	**2**	**3**	
Grade of Varices	I	5	5	1	11
	II	4	21	7	32
	III	0	16	9	25
	IV	0	4	8	12
	0	3	16	1	20
Total		12	62	26	100

$\chi 2$= 31.5 P=0.001 S

Patients were grouped according to Child Pugh Classification of Cirrhosis. The relationship between Child Pugh Grade and the grade of varices was studied and significant correlation noted(P=0.001).

TABLE 6 : RELATIONSHIP BETWEEN LAB PARAMETERS AND PRESENCE OF VARICES

Parameter	Varices	N	Mean	Std. Deviation	Student t-test
Serum Bilirubin	Present	80	2.371	2.1985	t=1.3 P=0.25
	Absent	20	1.765	1.7358	
	Total	100	2.250	2.1200	
Serum Albumin	Present	80	2.83	.739	t=0.01 P=0.98
	Absent	20	2.84	.670	
	Total	100	2.83	.723	
Hemoglobin	Present	80	9.291	2.8257	t=1.8 P=0.18
	Absent	20	8.345	2.8115	
	Total	100	9.102	2.8343	
Platelet Count	Present	80	96425.00	49847.051	t=12.8 P=0.001
	Absent	20	149600.00	89073.240	
	Total	100	107060.00	62947.921	
Spleen Bipolar Diameter	Present	80	171.61	40.988	t=6.6 P=0.01
	Absent	20	146.45	29.009	
	Total	100	166.58	40.055	

Relationship between non invasive parameters like Serum Bilirubin, Serum albumin, Hemoglobin, Platelet count, spleen Bipolar diameter to resence of varices was studied. Of this only Platelet Count (P=0.001) and Spleen Bipolar diameter (P=0.01) had statistical significance.

TABLE 7: RELATIONSHIP BETWEEN PORTAL VEIN SIZE AND PRESENCE OF VARICES

Parameter	Varices	N	Mean	Std. Deviation	Student t-test
Portal Vein Size	Present	80	14.091	4.4062	t=2.03
	Absent	20	12.230	3.4576	P=0.05

Significance was noted between Portal vein size(cm) and presence of Varices in the study group.

TABLE 8 : ASSOCIATION BETWEEN PC/SD RATIO AND PRESENCE OF VARICES

		Varices
PC/SD ratio	Pearson Correlation	-.482(**)
	Sig. (2-tailed)	.000
	N	100

** Correlation is significant at the 0.01 level (2-tailed).

There was statistically significant correlation between presence of varices and a platelet count/ splenic bipolar diameter ratio of ≤ 909.

0-0.2 poor correlation,0.2-0.4 fair,0.4-0.6 moderate,0.6-0.8 good, 0.8-1.0 Very good.

TABLE 9 : RELATIONSHIP BETWEEN PC/SD RATIO AND GRADE OF VARICES

		PC/SD RATIO		Total
		≤909	>909	
Grade of Varices	I	11	0	11
	II	28	4	32
	III	23	2	25
	IV	12	0	12
	0	10	10	20
Total		84	16	100

$\chi 2$= 23.1 P=0.001 S

Patients were categorized in to two groups based on cut off value of 909 for Platelet count / splenic diameter ratio. It's relation to the grade of varices was studied. A significant difference between the presence or absence of esophageal varices and platelet count to spleen diameter ratio of ≤909 was observed.

TABLE 10 : RELATIONSHIP BETWEEN ASCITES AND PRESENCE OF VARICES

Varices		Ascites			
		No		Yes	
		n	%	n	%
Varices	Present	53	82.8%	27	75.0%
	Absent	11	17.2%	9	25.0%

$\chi 2$= 0.88 P=0.35 NS

No significant association was obtained between presence of ascites and presence of varices in the study population.

TABLE 11 : RELATIONSHIP BETWEEN ASCITES AND GRADE OF VARICES

		Ascites		Total
		no	yes	
Grade of Varices	I	7	4	11
	II	24	8	32
	III	13	12	25
	IV	9	3	12
	0	11	9	20
Total		64	36	100

$\chi 2$= 4.57 P=0.33 NS

No significant association was noted between presence of ascites and grade of varices in our study group.

TABLE 12 : DISRTBUTION BASED ON SAAG VALUES

SAAG	Frequency	Percent
<1.1	14	38.9
1.1-1.44	9	25
1.45-1.99	11	30.6
>2	2	5.6
Total	36	

38.9 % of the patients had Serum ascetic albumin gradient (SAAG) < 1.1g/dl

SAAG > 1.1g/dl was seen in 61.1 % of the patients.

TABLE 13 : RELATIONSHIP BETWEEN SAAG AND PRESENCE OF VARICES

SAAG g/dl	Varices			
	Present		Absent	
	n	%	n	%
<1.1	5	18.5%	9	100.0%
>1.1	22	81.5%	0	

$\chi 2$= 10.86 P=0.001 S

81 % 0f the study population had varices when SAAG value was more than 1.1g/dl

All the patients in whom varices were absent had SAAG values less than 1.1g/dl.The two groups showed statistically significant difference (P= 0.001) based on presence and absence of varices.

TABLE 14: RELATIONSHIP BETWEEN SAAG AND GRADE OF VARICES

SAAG VALUES		Grade of Varices					Total
		I	**II**	**III**	**IV**	**0**	
SAAG	<1.1	1	4	0	0	9	14
g/dl	1.1-1.44	1	2	5	1	0	9
	1.45-1.99	2	1	6	2	0	11
	>2	0	1	1	0	0	2
Total		4	8	12	3	9	36

When the Value of SAAG was < 1.1g/dl it was noted that Grade III and IV varices were absent. When the SAAG values increased more than 1.1g/dl, there was considerable increase in grade III varices.

TABLE 15 : ASSOCIATION BETWEEN SAAG AND GRADE OF VARICES

		Varices
SAAG	Pearson Correlation	0..552(**)
	Sig. (2-tailed)	.000
	N	36

** Correlation is significant at the 0.01 level (2-tailed).

TABLE 16 : COORDINATES OF THE CURVE (ROC)

Test Result Variable(s): SAAG

Positive if Greater Than or Equal To(a)	Sensitivity	1 - Specificity
-.2000	1.000	1.000
.8500	.963	1.000
.9500	.889	.778
1.0500	.815	.333
1.1500	**.815**	**.000**
1.2500	**.778**	**.000**
1.3500	.667	.000
1.4500	.481	.000
1.5500	.407	.000
1.6500	.296	.000
1.7500	.222	.000
1.8500	.111	.000
1.9500	.074	.000
3.0000	.000	.000

The test result variable(s): SAAG has at least one tie between the positive actual state group and the negative actual state group.

a= The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

When cut off SAAG value was taken as 1.20± .05 gm/dl it was noted that the test achieved 100 % specificity and sensitivity ranging from 77.8 to 81.5 %.

TABLE 17 : ROLE OF PC/SD RATIO IN PREDICTING VARICES

		Varices		**Total**
		Present	**Absent**	
PC/SD RATIO	≤909	74	10	84
	>909	6	10	16
Total		80	20	100

	Value in %	95 % CI
Sensitivity	88	79-94
Specificity	63	35-85
False positive	38	15-65
False Negative	12	6-21
Positive Predictive Value	93	84-97
Negative Predictive Value	50	27-73

The sensitivity of PC/SD Ratio of ≤ 909 in predicting presence of esophageal varices was 88 %. It's positive predictive value is 93 %.

TABLE 18 : ROLE OF SAAG IN PREDICTING VARICES IN CIRRHOTIC PATIENTS WITH ASCITES

		Varices		Total
		Present	**Absent**	
SAAG	< 1.1	5	9	22
	> 1.1	22	0	14
Total		27	9	36

	Value in %	95 % CI
Sensitivity	81	62-94
Specificity	100	63-100
False positive	0	0-33
False Negative	19	6-38
Positive Predictive Value	100	85-100
Negative Predictive Value	64	35-87

The sensitivity of SAAG > 1.1 in predicting the presence of varices is 81 % and it's positive predictive value is 100 %.

TABLE 19 : UTILTY OF COMBINING SAAG AND PC/SD RATIO AS NON INVASIVE PARAMETERS FOR PREDICTING VARICES IN CIRRHOTIC PATIENTS WITH ASCITES

		PC/SD RATIO		Total
		≤909	>909	
SAAG	<1.1	11	3	14
	>1.1	20	2	22
Total		31	5	36

Parameter	Number of patients with Varices detected	Percentage detected
SAAG	22/36	61 %
SAAG AND PC/SD RATIO	20/31	66 %

DISCUSSION

Our study sample consisted of hundred patients of whom sixty were male and forty were females. The mean age was 41.85 (SD = 12.72). Distribution of grade of varices was studied in various age groups and no significant correlation was detected.(Table 1)

No significant gender difference in the distribution of grade of varices was found in our study.(Table 2).

We studied the frequency of distribution based on Conn's grading of varices and found that Grade II predominated (32 %). 20 % of the study population did not have varices.(Table 3; Figure 1).

Our study could not find any significant association between hepatic encephalopathy and varices.(Table 4).

Patients were grouped according to Child Pugh Classification of Cirrhosis. The relationship between Child Pugh Grade and the grade of varices was studied and significant correlation noted (P=0.001) (Table 5, Figure 2). Thus as patients progress to decompensated liver disease (CP Grade B & C) it is noted that the presence of varices increases.This is finding is consistent with study by Madhotra et al(2002),Zaman et al (2001).

Relationship between non invasive parameters like Serum Bilirubin, Serum albumin, Hemoglobin, Platelet count, spleen Bipolar diameter to presence of varices was studied. Among these only Platelet Count (P=0.001) and Spleen Bipolar diameter (P=0.01) had statistical significance. (Table 6)

The results indicating the relevance of platelet count are on par with studies by Thomopolos et al (2003), Madhotra et al (2002), Pilette et al (1999), Shepis et al(1999), Zaman et al (1999).Studies by Chalasani et al(1999), Sanjay Kumar et al (2006),Torres et al (1996) state that splenomegaly is an independent predictor of presence of varices.

Significance was noted between portal vein size (cm) and presence of varices. (Table 7)

Similar results were obtained in study by D'Amico et al (2004).

Patients were categorized in to two groups based on cut off value of 909 for Platelet count / splenic diameter ratio. It's relation to the grade of varices was studied. A significant difference between the presence or absence of esophageal varices and platelet count to spleen diameter ratio of 909 was observed. (P= 0.001) (Table 8,9)(Figure 3,4). This finding is in agreement with study by Gianni et al(2003). The use of Platelet count/ splenic diameter ratio overcomes the fallacy of using Platelet count alone in predicting esophageal varices for the reason that platelet count may decrease in chronic liver disease due to several other factors. This ratio is introduced to take in to consideration the decrease in platelet count which most likely depends on hypersplenism caused by portal hypertension. Performing unnecessary endoscopy in all patients can be avoided if we take a platelet count/ splenic diameter ratio cut off > 909, without running the risk of missing cases with esophageal varices .

Although Thomopolos et al (2003) have put forth ascites as an independent predictor of presence of large varices, our study does not demonstrate a statistically correlation between presence and grade of varices and ascites.(Table 10,11)

We grouped patients based on range of SAAG values. Of the study sample SAAG was less than 1.1 in 38.9 % of the patients and more than 1.1 in 61.1 %.(Table 12)

81 % 0f the study population had varices when SAAG value was more than 1.1

All the patients in whom varices were absent had SAAG values less than 1.1

The two groups showed statistically significant difference (P= 0.001) based on presence and absence of varices. (Table 13; figure 5 a & b). This is consistent with studies by Torres et al(1996), Gurubacharya et al (2005),Kajani et al(1990), Dittrich et al (2001).

We also assessed the correlation between grade of varices and SAAG values.(Table 14,15)(Figure 6 a & b)When the Value of SAAG was < 1.1 it was noted that Grade III and IV varices were absent. When the SAAG values increased more than 1.1, there was considerable increase in grade III varices.. In our study there was moderate correlation (r= 0.552) between SAAG and grade of varices. This finding is similar to the study by Torres et al(1996,1998). However, Gurubacharya et al(2005) and Demyrel et al (2003)

did not find out any correlation between degree of SAAG and grade of varices.

Receiver operating characteristic curve (ROC curves) (Figure 7)were used to assess the cut off value of SAAG with the best sensitivity and specificity for a diagnosis of esophageal varices. We found that when the cut off value of SAAG was taken as

1.20± .05 gm/dl it was noted that the test achieved 100 % specificity and sensitivity ranging from 77.8 to 81.5 %.

However Torres et al (1998) found that a SAAG value of more than or equal to 1.435±.015 gm/dl is a useful mean to predict the presence of esophageal varices in patients with ascites.

The sensitivity of PC/SD Ratio of ≤909 in predicting presence of esophageal varices was 88 % with 95 % CI 79-94% It's positive predictive value is 93 % with 95 % CI 84-97% (Table 17) However study by Gianni et al(2003) brought out a sensitivity of 100 % and specificity of 93 % if Platelet count /Splenic diameter ratio was used in predicting varices. Even though, in our study the sensitivity of the ratio was only 88%, it would still be a very good tool for screening since we cater to a bigger patient population and have restricted resources. Since Cirrhotic patients need regular follow up with repeated endoscopies, using PC/SD ratio cut off of 909 would help reduce the burden.

The sensitivity of SAAG > 1.1g/dl in predicting the presence of varices in the subgroup of patients with ascites was 81 %(95% CI; 62-94) and it's positive predictive value is 100 % (95 %CI 85 – 100).(Table 18) .

In the subgroup of 36 patients with ascites we attempted to combine the parameters

(SAAG > 1.1 and Platelet count/Splenic diameter ratio cut off ≤ 909) .We found that if only SAAG was taken in to account, varices were diagnosed in 61 % of the study group. If Platelet count/ Splenic diameter ratio cut off of ≤ 909 was also applied, varices were diagnosed in 66 %. Combining these two non invasive parameters in subgroup with ascites can increase the reliability of predicting esophageal varices. So these parameters can be used to regularly follow up the cirrhotic patients with ascites for the progression of grade of varices at appropriate intervals.

Thus use of these parameters may help identify patients with a low probability of esophageal varices who may not need endoscopy. This may help reduce costs and discomfort for these patients and the burden on endoscopy units.

SUMMARY AND CONCLUSIONS

Hundred patients with newly diagnosed cirrhosis without prior history of bleed were subjected to clinical evaluation. All patients underwent biochemical tests, like liver function tests, complete blood counts, renal function tests, prothrombin time, ultrasonography of the abdomen to confirm the presence of cirrhosis and to record the spleen bipolar diameter, portal vein size, ascites and presence of collaterals and Ascitic fluid analysis in patients with ascites . Upper GI endoscopy was done in all patients to confirm the presence of varices and also to grade them. We tried to identify non invasive parameters for predicting esophageal varices in Cirrhotic patients. We assessed the role of Platelet count/Splenic diameter ratio and SAAG for predicting esophageal varices in cirrhotic patients.

Presence of varices increases as patients progress to decompensated liver disease.(Child Pugh grade B & C).

Decrease in platelet count was found to be an predictor of esophageal varices in patients with cirrhosis.

Ultrasound parameters Spleen bipolar diameter and portal vein size also predict the presence of esophageal varices .

When a cut off value of Platelet count/ splenic diameter ratio of ≤ 909 was applied in order to take in to consideration the decrease in platelet count due to hypersplenism; it was found to be a good predictor of presence and grade of esophageal varices .

The sensitivity of PC/SD Ratio of ≤909 in predicting presence of esophageal varices was 88 % with it's positive predictive value was 93 %.

Value of Serum ascitic albumin gradient (SAAG) more than 1.1g/dl is found to be a predictor for presence and grade of esophageal varices .

The sensitivity of SAAG > 1.1g/dl in predicting the presence of varices in the subgroup of patients with ascites was 81 %and it's positive predictive value was100 %.

When the cut off value of SAAG was taken as 1.20± .05 gm/dl it was noted that the test achieved 100 % specificity and sensitivity ranging from 77.8 to 81.5 %.

If only SAAG was taken in to account, varices were diagnosed in 61 % of the cirrhotic patients with ascites. When Platelet count/ Splenic diameter ratio cut off of ≤ 909 was also applied, varices were diagnosed in 66 %.

Combining these two non invasive parameters in subgroup with ascites can increase the reliability of predicting esophageal varices.So these parameters can be used to regularly follow up the cirrhotic patients with ascites for the progression of grade of varices at specific intervals.

The use of Platelet count/ Splenic diameter ratio, SAAG and combination of these two non invasive parameters in appropriate subgroups of cirrhotic patients for screening and follow up of esophageal varices can substantially reduce the cost of health care and discomfort for patients as well as reduce burden on endoscopy units.

LIMITATIONS

1. Small sample size.
2. Prospective studies were not done to validate the role of predictive parameters.
3. Although we could show that combining the two non invasive parameters increased the percentage of varices being detected, the combined sensitivity could not be calculated because of inadequate sample size.

REFERENCES

1. Akriviadis EA, Kapnias D, Hadjigavriel M, et al.(1996) Serum/ascitesalbumin gradient: its value as a rational approach to the differential diagnosis of ascites. Scandinavian Journal Of Gastroenterology,
   31: 814-7.
2. Alba D, Torres E, Vazquez JJ.(1995) Sero-ascitic gradient of albumin: usefulness and diagnostic limitations. Annals Of Internal Medicine,12 (8):404-7.
3. Al-Knawy B.(1997) Etiology of ascites and diagnostic value of serum-ascites albumin gradient in non-alcohol liver disease.Annals Of Saudi Medicine, 17: 26-8.
4. Amarapurkar DN, Parikh SS, Shankaran K, et al.(1994)Correlation between splenomegaly and esophageal varices in patients with liver cirrhosis. Endoscopy,26:563.
5. Bhasin D K, Siyad I (2004). Variceal Bleeding and Portal Hypertension: New Lights on Old Horizon. Endoscopy, 36: 120-129.
6. Cakaloglu Y, Okten A, Yalcin S.(1990) Serum-ascites albumin concentration gradient (A-GRAD) in the prediction of portal hypertension in ascitic patients.Gastroenterology, 98(1):134-40.
7. Chalasani N, Imperiale TF, Ismail A, et al.(1999) Predictors of large esophageal varices in patients with cirrhosis. American Journal Of Gastroenterology, 94:3285–91.

8. Das BB, Purohit A, Acharya U, Utreskova E.(2001) Serum-ascites albumin gradient: a predictor of esophageal varices with ascites. Indian Journal Of Pediatrics,68: 511-4.
9. D'Amico G, De Franchis R,(2004) and a cooperative study group.Upper digestive bleeding in cirrhosis: post-therapeutic outcome and prognostic indicators.Hepatology,38:599–612.
10. D'Amico G, Garcia-Tsao G, Calés P, et al.(2001) Diagnosis of portal hypertension: how and when. In: De Franchis R, ed. Proceedings of the Third Baveno International Consensus Workshop on Definitions, Methodology and Therapeutic Strategies. Oxford: Blackwell Science :36–63.
11. D'Amico G, Luca A(1997). Portal hypertension. Natural history. Clinical-hemodynamics correlation. Prediction of the risk of bleeding. Baillieres Clinical Gastroenterology,11:243–56.
12. D'Amico G,Morabito A.(2004) Non invasive markers of esophageal varices: Another round,not the last.Hepatology,39(1):30-34.
13. D'Amico G, Pagliaro L, Bosch J.(1995) The treatment of portal hypertension: A meta- analytic review,22:332–54.
14. D'Amico G, Pasta L, Madonia S, Tarantino G, Mancuso A, Malizia G,Giannuoli GC, et al.(2001) The incidence of esophageal varices in cirrhosis .Gastroenterology,120:A2.
15. De Franchis R, Pascal JP, Ancona E, et al.(1992) Definitions, methodology and therapeutic strategies in portal hypertension. A Consensus Development Workshop, Baveno, Lake Maggiore, Italy, April 5 and 6, 1990. Journal Of Hepatology,15:256–61.

16. De Franchis R, Primignani M.(2001)Natural history of portal hypertension in patients with cirrhosis. Clinical Liver Disease,5:645–63.
17. Demyrel U,Karincaoglu U,Harpttuoqlu M,Ates M,Seckur Y,Yildrim B,Himioglu F.(2003) Two findings of portal hypertension: Evaluation of correlation between serum-ascites albumin concentration gradient and esophageal varices in non alcoholic cirrhosis.Turkish Journal Of Gastroenterology,14(4):219-222.
18. Diseases of the liver: Leon Schiff and Eugene Schiff
19. Dittrich S, Yordi LM, de Mattos AA.(2001) The value of serum-ascites albumin gradient for the determination of portal hypertension in the diagnosis of ascites. Hepatogastroenterology, 48(37):166-8.
20. Fevery J; Nevens F.(2000) Esophageal varices: assessment of the risk of bleeding and mortality. Journal of gastroenterology and hepatology, 15(8):842-8.
21. Fleig WE.(2001) To scope or not to scope: still a question. Hepatology,33:471–2.
22. Fook-Hong NG, Siu-Yin W, Ching-Hong L, Kwong -Ming L, Chi-WingL, Chi-Sing C.(1999) Prediction of esophageal varices in patients with liver cirrhosis. Journal Of Gastroenterology Hepatology, 14:785–790.
23. Freeman JG, Darlow S, Cole AT.(1999) Platelet count as a predictor for the presence of oesophageal varices in alcoholic cirrhotic patients. Gastroenterology,116:A1211.

24. Garcia-Tsao G, Escorsell A, Zakko M, et al.(1997) Predicting the presence of significant portal hypertension and varices in compensated cirrhotic patients. Hepatology ,26:360A.

25. Garceau AJ, Chalmers TC.(1963) The Boston Inter-Hospital Liver Group. The natural history of cirrhosis: I. Survival with esophageal varices. New England Journal Of Medicine,268:469–73.

26. Giannini E, Botta F, Borro P, Risso D,Romagnoli P, Fasoli A, Mele M R,Testa E, Mansi C, Savarino V, Testa R.(2003)Platelet count/spleen diameter ratio: proposal and validation of a non-invasive parameter to predict the presence of esophageal varices in patients with liver cirrhosis.Gut,52:1200-1205.

27. Goh SH; Tan WP; Lee SW.(2005) Clinical predictors of bleeding esophageal varices in the ED.American Journal Of Emergency Medicine, 23(4):531-5.

28. Gorka W, Al Mulla A, Al Sebayel M, et al.(1997) Qualitative hepatic venous Doppler sonography versus portal flow-metry in predicting the severity of esophageal varices in hepatitis C cirrhosis. American Journal Of Roentgenology,169:511–5.

29. Goyal AK, Goyal SK, Pokharna DS, Sharma SK.(1989) Differential diagnosis of ascitic fluid: evaluation and comparison of various biochemical criteria with a special reference to serum ascites albumin concentration gradient and its relation to portal pressure. Tropical Gastroenterology, 10(1):51-5.

30. Grace ND, Groszmann RJ, Garcia-Tsao G, et al.(1998) Portal hypertension and variceal bleeding: an AASLD single topic symposium. Hepatology,28:868–80.

31. Graham D, Smith JL (1981)The course of patients after variceal hemorrhage. Gastroenterology,80:800–9.

32. Gurubacharya DL, Mathura KC, Karki DB.(2005) Correlation between serum-ascites albumin concentration gradient and endoscopic parameters of portal hypertension. Katmandu University Medical Journal (KUMJ),3(12):327-33.

33. Harjai KJ, Kamble MS, Ashar VJ, Anklesaria PS, Ratnam KL, Abraham P.(1995) Portal venous pressure and the serum-ascites albumin concentration gradient.Cleveland Clinical Journal Of Medicine,62(1):62-7.

34. Harrison's principles of Internal Medicine 16th edition.

35. Hoefs JC.(1983) Serum protein concentration and portal pressure determine the ascitic fluid protein concentration in patients with chronic liver disease.Journal Of Laboratory And Clinical Medicine, 102(2):260-73.

36. Ishibashi H; Higuchi N; Shimamura R; Hirata Y; Kudo J; Niho Y.(1991) Sonographic assessment and grading of spleen size. Journal of clinical ultrasound : JCU, 19(1): 21-5.

37. Jensen DM.(2002) Endoscopic screening for varices in cirrhosis: findings, implications, and outcomes. Gastroenterology,122:1620–30.

38. Jorge Marrero, Fernando J. Martinez and Robert Hyzy.(2003) Advances in Critical Care Hepatology. American Journal of Respiratory and Critical Care Medicine, 168:1421-1426.

39. Juan Turnes, Juan Carlos Garcia-Pagan, Juan G. Abraldes, Manuel Hernandez-Guerra, Alessandra Dell'Era, and Jaime Bosch.(2006) Pharmacological Reduction of Portal Pressure and Long-Term Risk of First Variceal Bleeding in Patients with Cirrhosis. American Journal of Gastroenterology,101:506–512.

40. Kajani MA, Yoo YK, Alexander JA, Gavaler JS, Stauber RE, Dindzans VJ, Van Thiel DH.(1990) Serum-ascites albumin gradients in nonalcoholic liver disease. Digestive Disease Science,35(1):33-7.

41. Lavergne J, Molina E, Reddy KR, et al.(1997) Ascites predicts the presence of high grade varices by screening gastroscopy. Gastrointestinal Endoscopy, 45:AB187.

42. Madhotra R, Mulcahy HE, Willner I, et al.(2002) Prediction of esophageal varices in patients with cirrhosis,Journal Of Clinical Gastroenterology, 34:81–5.

43. McCormick PA. The spleen, hypersplenism, and other relationships between the liver and spleen. In: Bircher J, Benhamou J-P, McIntyre N, et al, eds. Oxford Textbook of Clinical Hepatology. Oxford: Oxford University Press, 1999:787–95.

44. McHutchison JG.(1997) Differential diagnosis of ascites. Seminars In Liver Disease, 17: 191-202.

45. Mene A, Sharma D, Raina VK.(2003) Correlation between serum-ascites albumin concentration gradient with gastrointestinal bleeding in patients of portal hypertension. Tropical Doctors,33(1):39-41.

46. Ng FH, Wong SY, Loo CK, et al.(1999)Prediction of esophagogastric varices in patients with cirrhosis. Journal Of Gastroenterology Hepatology 14:785–90.

47. Ong J, Younossi ZM.(1999) Clinical predictors of large esophageal varices: how accurate are they? American Journal Of Gastroenterology,94:3103–5.

48. Pare P, Talbot J, Hoefs JC.(1983) Serum-ascites albumin concentration gradient: a physiologic approach to the differential diagnosis of ascites.Gastroenterology, 85(2):240-4.

49. Peck-Radosavljevic M.(2000) Thrombocytopenia in liver disease. Canadian Journal Of Gastroenterology,14(suppl D):60–6D.

50. Pilette C, Oberti F, Aubé C, et al.(1999) Non-invasive diagnosis of esophageal varices in chronic liver disease. Journal Of Hepatology,31:867–73.

51. Rajvanshi P, Kowdley KW.(2002) Prediction of varices in patients with cirrhosis. A high- stakes numbers game? Journal Of Clinical Gastroenterology,34:4–5.

52. Rector WG Jr, Reynolds TB.(1984) Superiority of the serum-ascites albumin difference over the ascites total protein concentrationin separation of "transudative" and "exudative"ascites. American Journal Of Medicine,77: 83-5.

53. Riggio O, Angeloni S, Nicolini G, et al.(2002) Endoscopic screening for esophageal varices in cirrhotic patients. Hepatology,35:501–2.

54. Rigo GP, Merighi A, Chalen JN, et al.(1992) A prospective study of the ability of three endoscopic classifications to predict hemorrhage from esophageal varices. Gastrointestinal Endoscopy,38:425–9.

55. Runyon BA, Montano AA, Akriviadis EA, et al.(1992) The serum ascites albumin gradient is superior to the exudate-transudate concept in the differential diagnosis of ascites. Annals Of Internal Medicine, 117: 215-20.

56. Sanjay Kumar Sharma and Rakesh Aggarwal.(2006) Prediction of large esophageal varices in patients with cirrhosis of the liver using clinical, laboratory and imaging parameters. Journal of Gastroenterology and Hepatology,Online Early Issue.

57. Schepis F, Cammà C, Niceforo D, et al.(2001) Which patients should undergo endoscopic screening for esophageal varices detection? Hepatology,33:333–8.

58. Slesinger and Fordtran's Gastro intestinal liver disease. Seventh Edition.

59. Sheila Sherlock , James Dooley. Diseases of the liver and biliary system. Eleventh Edition.

60. Thomopoulos K C, Labropoulou-Karatza C,Mimidis K P, Katsakoulis E C, Iconomou G, Nikolopoulou V N.(2003)Non invasive predictors of the presence of large esophageal varices in patients with cirrhosis. Digestive and liver disease,35(7):473-78.

61. Torres E, Barros P, Calmet F.(1998). Correlation between serum-ascites albumin concentration gradient and endoscopic parameters of portal hypertension. American Journal Of Gastroenterology,93(11):2172-8.

62. Torres E, Calmet F, Barros P.(1996) Endoscopic and clinical parameters in assessing th degree of portal hypertension: the value of the serum-ascitic fluid albumin gradient. Review Of Gastroenterology Peru,16(1):20-6.

63. Torres E, Calme F, Herrera B.(1996) Echographic parameters in the evaluation of the degree of portal hypertension. Review Of Gastroenterology Peru, 16(2):125-32.

64. Zaman A, Becker T, Lopidus J, et al.(2001)Risk factors for the presence of varices in cirrhotic patients without a history of variceal hemorrhage. Archives Of Internal Medicine,161:2564–70.

65. Zaman A, Hapke R, Flora K, et al.(1999) Factors predicting the presence of esophageal varices or gastric varices in patients with advanced liver disease. American Journal Of Gastroenterology,94:3292–6.

66. Zeijen RNM, Caenepeel P, Stockbrügger RW, et al.(1994) Prediction of esophageal varices in liver disease: preliminary results. Gastroenterology,106:A1013.

67. Zhu XH, Liu B, Cheng ZY.(2003) Diagnostic value of serum-ascites albumin gradient. Hunan Yi Ke Da Xue Xue Bao, 28(3):278-80.

PROFORMA

S. No: IP No: Address:

Name: Age: Sex:

Unit/Ward:

CLINICAL FEATURES	
Hemetemesis	
Malena	
Bleeding PR	
Bleeding tendencies	
Anaemia	
Jaundice	
Pedal Oedema	
Stigmata of CLD	
Dilated veins	
Hepatomegaly	
Splenomegaly	
Ascites	
Encephalopathy	

ASCITIC FLUID ANALYSIS	
Cells	
Protein (g/dL)	
SAAG	

USG ABDOMEN	
Cirrhosis	
Spleen bipolar Diameter (mm)	
Portal Vein size (cm)	
Splenic Vein (cm)	
Ascites	
Collaterals	

COMPLETE HEMOGRAM	
Hb (g/dL)	
TC (cells/cmm)	
DC	
RBC(millions/cmm)	
Platelet(Lakhs/cmm)	
MCV(fL)	
MCHC(g/dL)	
PCV	
Clotting Time(sec)	
Bleeding time(sec)	
Peripheral smear	

OGD SCOPY	
Varices	
Grade	
Others	

PAST & PERSONAL H/O	
Jaundice	
Alcoholism	
Blood Transfusion	
Hepatotoxic Drugs	
Tattooing/IV drug	

BLOOD BIOCHEMISTRY	
Blood Sugar(mg/dL)	
Blood Urea(mg/dL)	
S. Creatinine(mg/dL)	
S.Proteins(g/dL) T	
A	
G	
S. Bilirubin(mg/dL) T	
D	
ID	
SGOT(IU/L)	
SGPT(IU/L)	
SAP(IU/L)	
Prothrombin Time(sec)	

CHILD PUGH CLASSIFICATION			
	A	B	C
S. Bilirubin	<2.0	2-3	>3
S. Albumin	>3.5	2.8-3.5	<2.8
Ascites	None	Slight or Controlled	Moderate or Uncontrolled
Encephalopathy	None	Minimal	Coma
ProthrombinTime(sec) Or INR	0-4 <1.7	4-6 1.7-2.3	>6 >2.3

Platelet Count/Spleen Diameter Ratio –

Oesophageal Varices –

SAAG -

FIGURE 1: DISTRIBUTION BASED ON GRADING OF VARICES

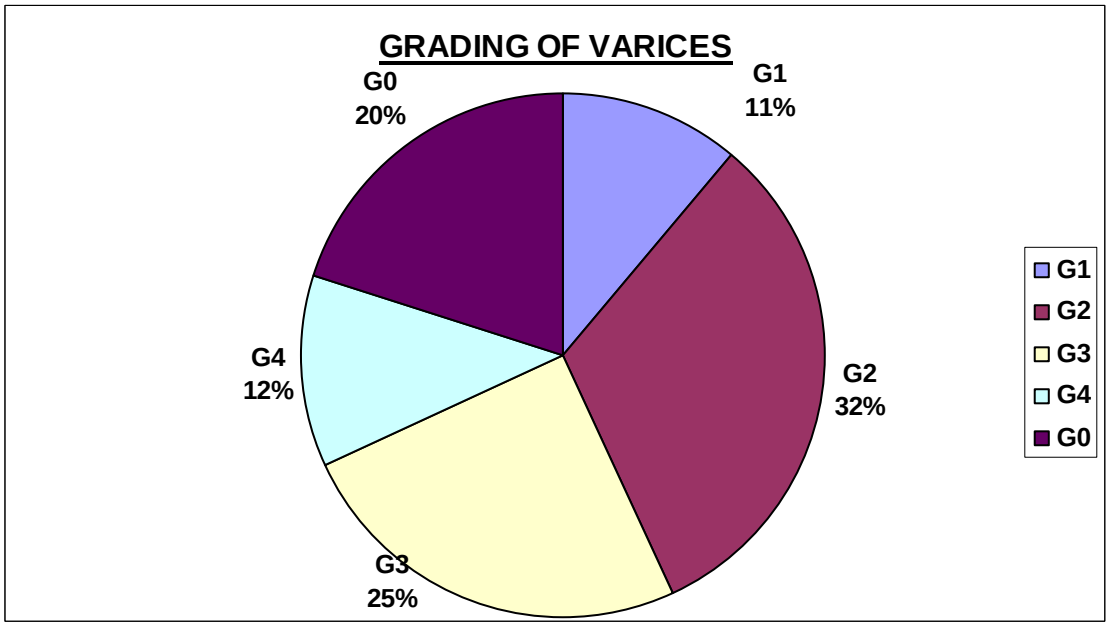


FIGURE 2: RELATIONSHIP BETWEEN CHILD PUGH GRADE AND VARICES

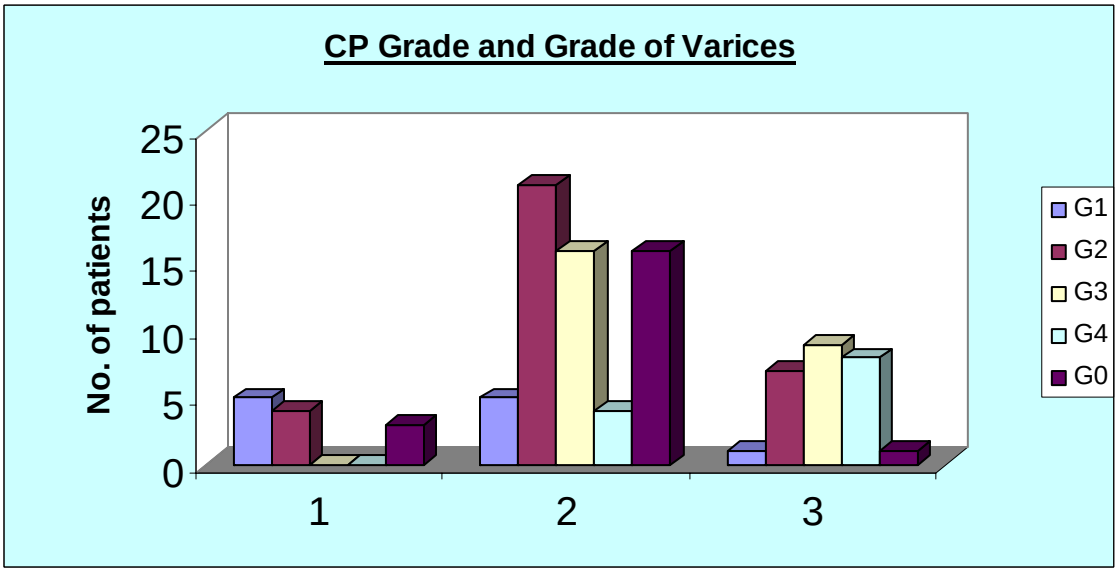


FIGURE 3:CORRELATION BETWEEN GRADE OF VARICES AND PC/SD RATIO

Grade o of varice coded as 9 in the figure

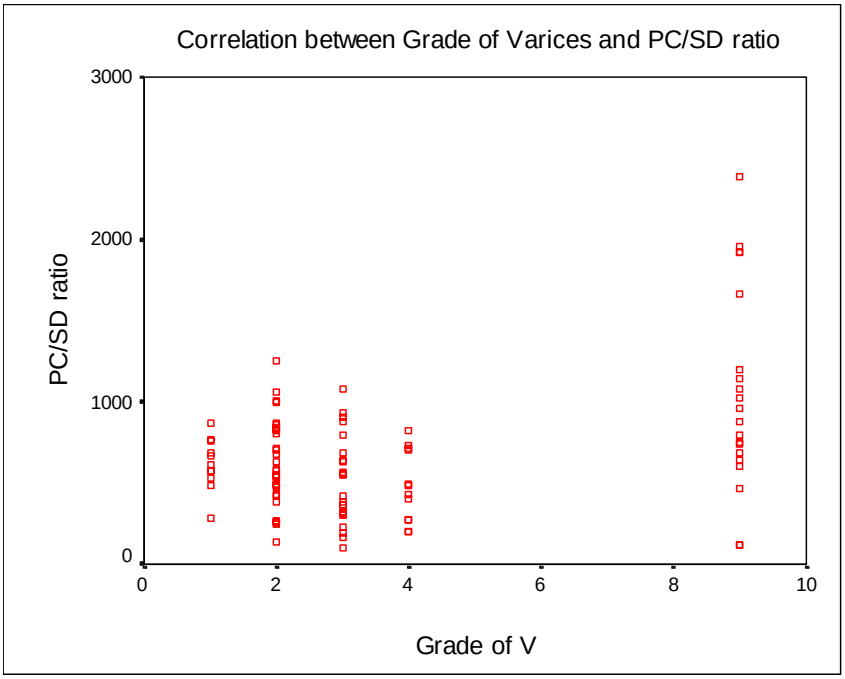


FIGURE 4: RELATIONSHIP BETWEEN PC/SD RATIO AND GRADE OF VARICES

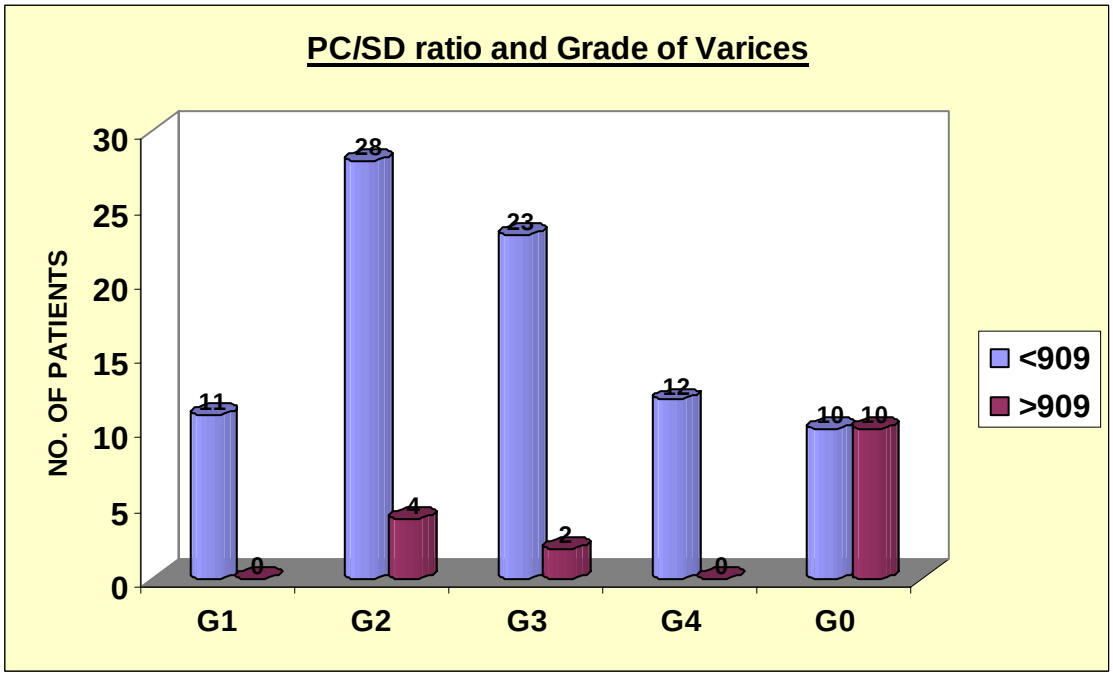
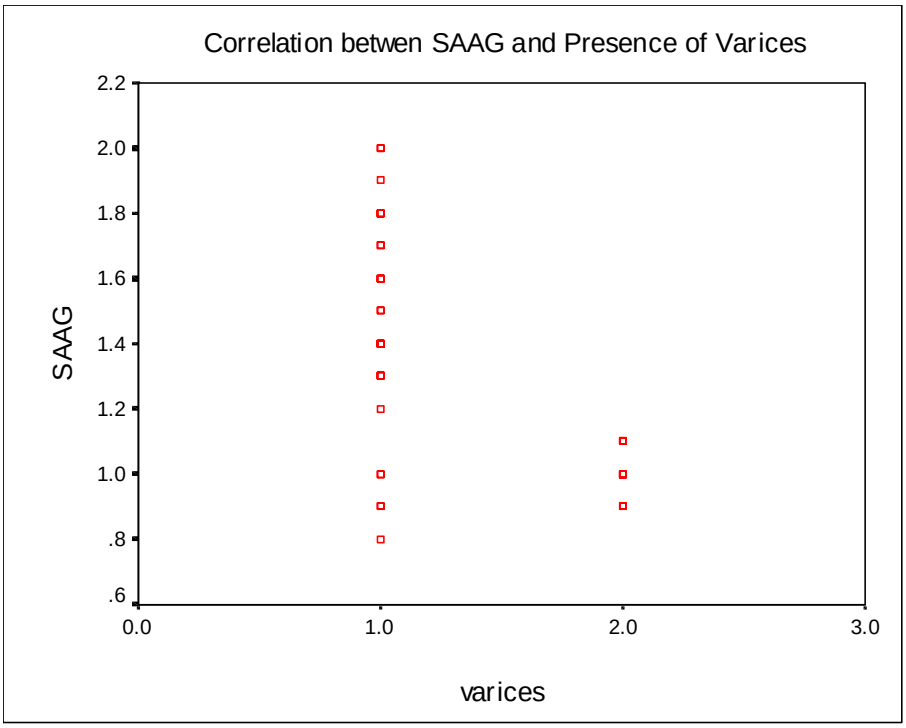


FIGURE 5 : RELATIONSHIP BETWEEN SAAG AND PRESENCE OF VARICES

1= Varices present
2= Varices absent

(a)



(b)

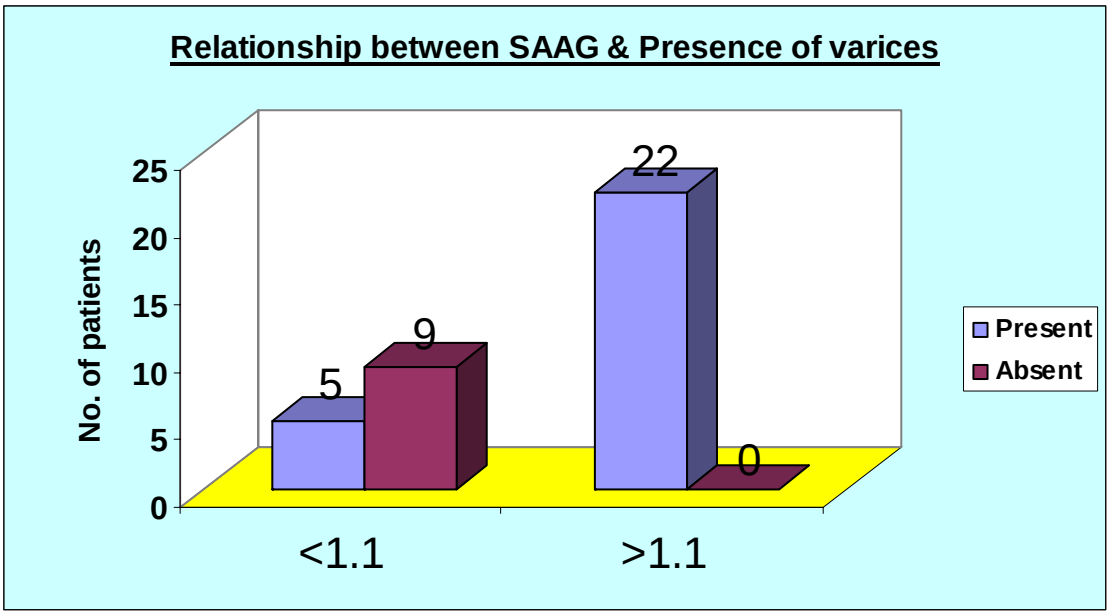
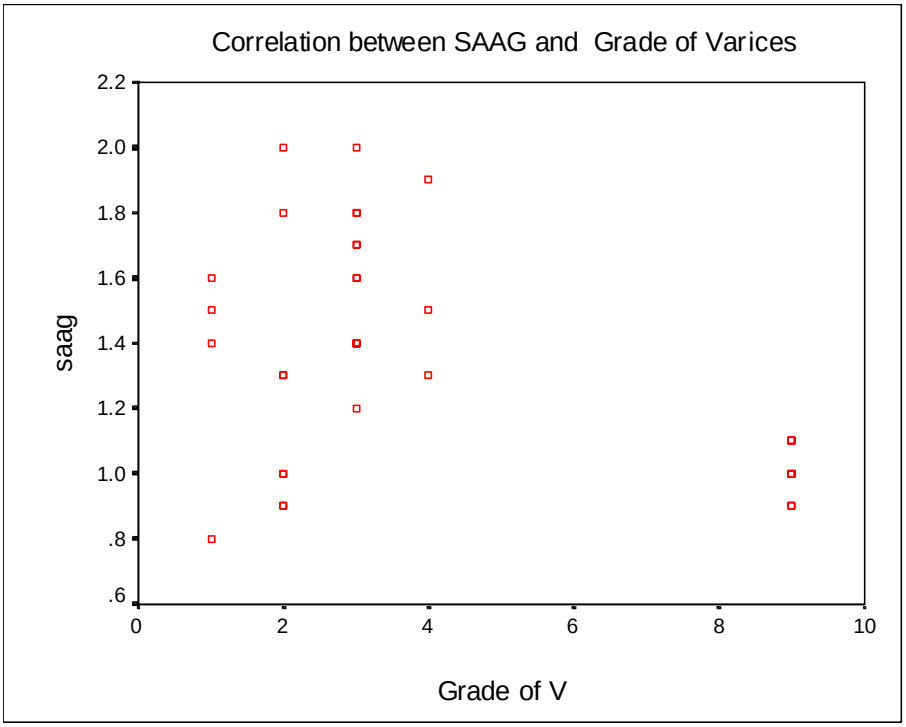


FIGURE 6 : RELATIONSHIP BETWEEN SAAG AND GRADE OF VARICES

Grade o of varice coded as 9 in the figure

(a)



(b)

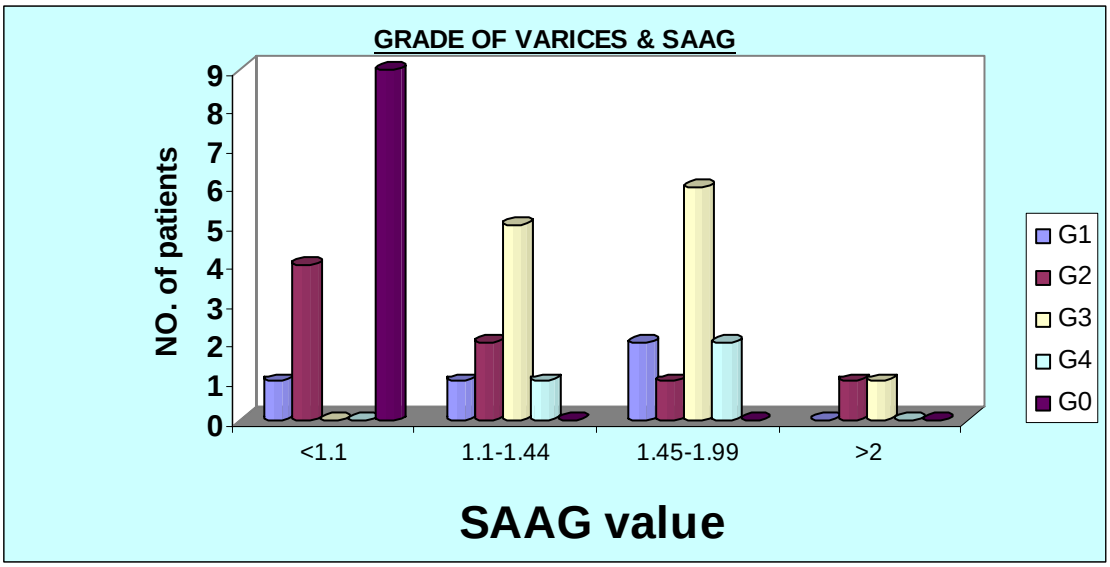


FIGURE 7: ROC CURVE FOR SAAG